

App 9/20/02 PD

Specific Species 03/6

(Audit 10/650,006)

(INVENTION)

09/29/2005

L638 ANSWER 89 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-44420 DRUGU P

TITLE: Differential effect of retinoic acid on growth regulation by phorbol ester in human cancer cell lines.

AUTHOR: Agadir A; Chen G Q; Bost F; Li Y; Mercola D; Zhang X K

LOCATION: La Jolla; San Diego, Cal., USA

SOURCE: J.Biol.Chem. (274, No. 42, 29779-85, 1999) 8 Fig. 1 Tab. 49

Ref.

CODEN: JBCHA3

ISSN: 0021-9258

AVAIL. OF DOC.: The Burnham Institute, Cancer Research Center, 10901 N. Torrey Pines Rd., La Jolla, CA 92037, U.S.A. (X.K.Z.).
(e-mail: xzhang@burnham-inst.org).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB All-trans-retinoic acid (trans-RA) inhibited growth of human breast cancer ZR75-1 and T47D cells and lung cancer H460 and H292 cells, while phorbol ester 12-O-tetra decanoyl phorbol-13-acetate (TPA) inhibited growth of H460 and H292 cells, but induced ZR75-1 cell growth. Trans-RA nonsignificantly regulated the inhibitory effect of TPA, but completely prevented its stimulatory effect. In H460 and H292 cells, TPA effect was associated with induction of G0/G1 arrest, and in ZR75-1 cells with inhibition of G0/G1 arrest with increase of S phase. Trans-RA did not affect TPA-induced p21WAF1 expression but inhibited TPA-induced AP-1 activity in ZR75-1 cells and the constitutive AP-1 activity in H460 and H292 cells. Trans-RA modulates TPA activity through TPA-induced **c-Jun N-terminal kinase** (JNK)/AP-1 pathway.

L638 ANSWER 90 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-31988 DRUGU B V

TITLE: Suppression of apoptosis by all-trans-retinoic acid.

AUTHOR: Moreno Manzano V; Ishikawa Y; Lucio Cazana J; Kitamura M

CORPORATE SOURCE: Univ.London; Univ.Alcala-de-Henares

LOCATION: London, U.K.; Madrid, Esp.

SOURCE: J.Biol.Chem. (274, No. 29, 20251-58, 1999) 4 Fig. 75 Ref.

CODEN: JBCHA3

ISSN: 0021-9258

AVAIL. OF DOC.: Glomerular Bioengineering Unit, Dept. of Medicine, University College London Medical School, The Rayne Institute, 5 University St., London WC1E 6JJ, England. (e-mail: m.kitamura@medicine.ucl.ac.uk).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The suppression of apoptosis by all-trans-retinoic acid (t-RA, tretinoin, Sigma-Chemical) was investigated in cell lines in-vitro. Pretreatment of mesangial cells (SM43) with t-RA (0.1-7.5 uM) attenuated the morphological and biochemical hallmarks of apoptosis induced by hydrogen peroxide and pyrrolidine dithiocarbamate. Suppression of hydrogen peroxide-induced apoptosis was also seen in NRK49F fibroblasts. The t-RA abrogated the hydrogen peroxide-induced expression c-fos/c-jun and activation of activator protein (AP)-1, and inhibited the activation of **c-Jun N-terminal kinase** (JNK). The findings suggest that the JNK-AP-1 pathway is 1 of the potential targets of t-RA. (No EX).

L638 (ANSWER 91 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1999-40477 DRUGU P V E

TITLE: Hormone-activated nuclear receptors inhibit the stimulation of the JNK and ERK signalling pathways in endothelial cells.
AUTHOR: Gonzalez M V; Gonzalez Sancho J M; Caelles C; Munoz A; Jimenez B
CORPORATE SOURCE: Univ.Madrid; Univ.Barcelona
LOCATION: Madrid; Barcelona, Esp.
SOURCE: FEBS Lett. (459, No. 2, 272-76, 1999) 4 Fig. 50 Ref.
CODEN: FEBLAL ISSN: 0014-5793
AVAIL. OF DOC.: Instituto de Investigaciones Biomedicas 'Alberto Sols', Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Arturo Duperier 4, E-28029 Madrid, Spain. (A.M.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Dexamethasone (DEX) and retinoic acid (RA, tretinoin, both Sigma-Chemical) were shown to inhibit the activation of **c-Jun N-terminal kinase** (JNK) and extracellular regulated kinase (ERK) signalling pathways by TNFalpha and vascular endothelial growth factor (VEGF) in HMEC-1, EOMA and MS-1 endothelial cells in-vitro. DEX and RA did not inhibit the activation of the p38 mitogen-activated protein kinase cascade. The antagonism with AP-1 transcription factor may underlie at least partially the anti-angiogenic effect of glucocorticoids and retinoids.

L638 ANSWER 92 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1998-20251 DRUGU P B V

TITLE: All-trans-retinoic acid inhibits Jun N-terminal kinase-dependent signaling pathways.

AUTHOR: Lee H Y; Walsh G L; Dawson M I; Hong W K; Kurie J M

CORPORATE SOURCE: Univ.Texas-Syst.; Scripps-Res.Inst.

LOCATION: Houston, Tex.; Menlo Park, Cal., USA

SOURCE: J.Biol.Chem. (273, No. 12, 7066-71, 1998) 5 Fig. 46 Ref.

CODEN: JBCHA3 ISSN: 0021-9258

AVAIL. OF DOC.: Box 80, Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, U.S.A. (J.M.K.).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB All-trans retinoic acid (t-RA, Sigma-Chemical) was an in-vitro inhibitor of **c-Jun N-terminal kinase** (JNK), and to a lesser extent, extracellular signal-regulated kinase (ERK) activities in human bronchial epithelial cells. t-RA suppressed c-fos gene transcription in the cells. Use of Ro-13-7410, Ro-41-5253, (2E,4E,6Z)-3-methyl 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl 3-propyloxy-2-naphthalenyl) 2,4,6-heptatrienoic acid (LGD-100754) (all Ligand-Pharm.) and 2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl 2-naphthalenyl)-2-(4-carboxyphenyl) 1,3-oxathiolane (SR-11235) showed that RA receptor-alpha (RAR-alpha) and all retinoid X receptors (RXR) were involved in t-RA suppression of c-fos promoter activity. PD-98059 (Calbiochem) was used.

L638 ANSWER 93 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 1997-40458 DRUGU P B V

TITLE: The transcription factor c-Jun is critical for ultraviolet irradiation-induced premature skin aging and its prevention by retinoic acid in human skin in vivo.

AUTHOR: Fisher G J; Talwar H S; Li X Y; McPhillips F; Lin P; Kang S;

Voorhees J J
CORPORATE SOURCE: Univ.Michigan
LOCATION: Ann Arbor, Mich., USA
SOURCE: J.Invest.Dermatol. (109, No. 3, 410, 1997)
CODEN: JIDEAE ISSN: 0022-202X
AVAIL. OF DOC.: Department of Dermatology, University of Michigan, Ann Arbor,
MI, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB The mechanisms of matrix metalloproteinases (MMPs) induction by UV, and its antagonism by retinoic acid (RA) were investigated in human skin in-vivo. Skin was obtained 15 min to 72 hr after irradiation and analyzed for upstream signalling molecules, and transcription factor AP-1, which are responsible for induction of MMP gene expression. The data describe a UV-induced molecular pathway leading to induction and activation of c-jun, which acts in concert with c-fos to drive MMP gene expression in human skin in-vivo. RA antagonizes this pathway, through a novel mechanism involving reduced translation and/or increased degradation of c-jun. Thus, c-jun is a critical molecular mediator of UV-induced dermal damage, and its prevention by RA. (conference abstract).

L638 ANSWER 94 OF 94 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 1999:500686 SCISEARCH
THE GENUINE ARTICLE: 212BK
TITLE: Protein kinase C delta is essential for etoposide-induced apoptosis in salivary gland acinar cells
AUTHOR: Reyland M E (Reprint); Anderson S M; Matassa A A; Barzen K A; Quissell D O
CORPORATE SOURCE: Univ Colorado, Hlth Sci Ctr, Dept Basic Sci & Oral Res, Sch Dent, 4200 E 9th Ave, Box C286, Denver, CO 80262 USA (Reprint); Univ Colorado, Hlth Sci Ctr, Dept Basic Sci & Oral Res, Sch Dent, Denver, CO 80262 USA; Univ Colorado, Hlth Sci Ctr, Sch Med, Dept Pathol, Denver, CO 80262 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2 JUL 1999)
Vol. 274, No. 27, pp. 19115-19123.
ISSN: 0021-9258.
PUBLISHER: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814 USA.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 58
ENTRY DATE: Entered STN: 1999
Last Updated on STN: 1999
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

ED Entered STN: 1999
Last Updated on STN: 1999

AB We have previously shown that parotid C5 salivary acinar cells undergo apoptosis in response to etoposide treatment as indicated by alterations in cell morphology, caspase-3 activation, DNA fragmentation, sustained activation of c-Jun N-terminal kinase, and inactivation of extracellular regulated kinases 1 and 2. Here we report that apoptosis results in the caspase-dependent cleavage of protein kinase C-delta (PKC delta) to a 40-kDa fragment, the appearance of which correlates with a 9-fold increase in PKC delta activity. To understand the function of activated PKC delta in apoptosis, we have used

the PKC delta-specific inhibitor, rottlerin, Pretreatment of parotid C5 cells with rottlerin prior to the addition of etoposide blocks the appearance of the apoptotic morphology, the sustained activation of **c-Jun N-terminal kinase**, and inactivation of extracellular regulated kinases 1 and 2, Inhibition of PKC delta also partially inhibits caspase-3 activation and DNA fragmentation. Immunoblot analysis shows that the PKC delta cleavage product does not accumulate in parotid C5 cells treated with rottlerin and etoposide together, suggesting that the catalytic activity of PKC delta may be required for cleavage. PKC alpha and PKC beta 1 activities also increase during etoposide-induced apoptosis, Inhibition of these two isoforms with Go6976 slightly suppresses the apoptotic morphology, caspase-3 activation, and DNA fragmentation, but has no effect on the sustained activation of **c-Jun N-terminal kinase** or inactivation of extracellular regulated kinase 1 and 2, These data demonstrate that activation of PKC delta is an integral and essential part of the apoptotic program in parotid C5 cells and that specific activated isoforms of PKC may have distinct functions in cell death.

=> d que 178

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L56 (      3)SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L57 (      1)SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L58      SEL  PLU=ON  L56 1- CHEM :      11 TERMS
L59 (    432)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L58
L60 (    186)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L56
L61      SEL  PLU=ON  L57 1- CHEM :      13 TERMS
L62 (   4144)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L61
L63 (    931)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L57
L64 (   35883)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE"+PFT,NT/CT
L65 (   21166)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE OR DISORDER"+PFT
      ,NT/CT
L66 (   17731)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYES, DISEASES OR DISORDERS"+
      PFT,NT/CT
L67 (    610)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE (L) DRY"+PFT,NT/
      CT
L68 (      3)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60) AND (L64 OR L65
      OR L66 OR L67)
L69 (    27)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L62 OR L63) AND (L64 OR L65
      OR L66 OR L67)
L70      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
      R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
      CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L71 (      1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60) (L) L70
L72 (     24)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L62 OR L63) (L) L70
L73 (     47)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L68 OR L69 OR L71 OR L72
L74 (     65)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L59 OR L60 OR L62 OR L63)
      AND L70
L75 (     68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L73 OR L74)
L76 (      5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L75 AND (L59 OR L60)
L77 (      3)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L76 AND (AY<2003 OR PY<2003
      OR PRY<2003)
L78      2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L76 NOT L77

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=> d que 1186

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L171(      8)SEA FILE=WPIX ABB=ON  PLU=ON  (RA8XOT/DCN OR RA8XOT-D/DCN OR
      RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
L172(      8)SEA FILE=WPIX ABB=ON  PLU=ON  RA8XOT/M0,M1,M2,M3,M4,M5,M6
L173(      8)SEA FILE=WPIX ABB=ON  PLU=ON  L171 OR L172
L174(   3915)SEA FILE=WPIX ABB=ON  PLU=ON  A61P027-02/IPC
L175(  16334)SEA FILE=WPIX ABB=ON  PLU=ON  (B14-N03 OR C14-N03 OR E14-N03
      OR B12-J08 OR C12-J08 OR E12-J08)/MC
L176(      1)SEA FILE=WPIX ABB=ON  PLU=ON  L173 AND (L174 OR L175)
L177(      3)SEA FILE=WPIX ABB=ON  PLU=ON  L173 AND (EYE/BIX OR EYES/BIX OR
      OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
      OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
      ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
      LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
      AL?/BIX)
L178(      8)SEA FILE=WPIX ABB=ON  PLU=ON  L173 OR L176 OR L177
L179(   819)SEA FILE=WPIX ABB=ON  PLU=ON  (JNK/BIX OR JNK1/BIX OR P46JNK/BI
      X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
L180(   115)SEA FILE=WPIX ABB=ON  PLU=ON  L179 AND (L174 OR L175)
L181(   105)SEA FILE=WPIX ABB=ON  PLU=ON  L180 AND (EYE/BIX OR EYES/BIX OR
      OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
      OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
      ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
      LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH

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AL?/BIX)
L182(      28)SEA FILE=WPIX ABB=ON  PLU=ON  L181 AND ((DRY?(3A)EYE?) OR
           ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR
           ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN?
           OR ?XEROPH?)/BIX
L183(      35)SEA FILE=WPIX ABB=ON  PLU=ON  L178 OR L182
L184(      28)SEA FILE=WPIX ABB=ON  PLU=ON  L183 AND (AY<2003 OR PY<2003 OR
           PRY<2003)
L185(      5)SEA FILE=WPIX ABB=ON  PLU=ON  L184 AND L178
L186      3 SEA FILE=WPIX ABB=ON  PLU=ON  L178 NOT L185

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=> d que 1222

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L218(      3)SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L219      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L220      SEL PLU=ON  L218 1- CHEM :      11 TERMS
L221(      218)SEA FILE=MEDLINE ABB=ON  PLU=ON  L220
L222      1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L221 AND L219

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=> d que 1255

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L246(      3)SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L247      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L248      SEL PLU=ON  L246 1- CHEM :      11 TERMS
L249(      547)SEA FILE=EMBASE ABB=ON  PLU=ON  L248
L250(      2325)SEA FILE=EMBASE ABB=ON  PLU=ON  "DRY EYE"+PFT,NT/CT
L251(      0)SEA FILE=EMBASE ABB=ON  PLU=ON  L249 AND L250
L252(      1)SEA FILE=EMBASE ABB=ON  PLU=ON  L249 AND L247
L253(      1)SEA FILE=EMBASE ABB=ON  PLU=ON  (L251 OR L252)
L254(      0)SEA FILE=EMBASE ABB=ON  PLU=ON  L253 AND (PY<2003 OR MY<2003)
L255      1 SEA FILE=EMBASE ABB=ON  PLU=ON  L253 NOT L254

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=> d his 1479

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(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
VETU, VETB, SCISEARCH' ENTERED AT 07:43:51 ON 29 SEP 2005)
L479      5 SEA L380 NOT L458

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=> d que 1479

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L376      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L377      SEL PLU=ON  L376 1- CHEM :      11 TERMS
L378(      813)SEA L377
L379(      6)SEA L378 AND L376
L380(      6)DUP REM L379 (0 DUPLICATES REMOVED)
L381      SEL PLU=ON  L376 1- CHEM :      13 TERMS
L382(      13886)SEA L381
L383(      139)SEA L382 AND L376
L384(      88)DUP REM L383 (51 DUPLICATES REMOVED)
L385(      55)SEA FILE=BIOSIS L384
L386(      25)SEA FILE=BIOSIS L385 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR

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LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L387 (6)SEA FILE=TOXCENTER L384

L388 (2)SEA FILE=TOXCENTER L387 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L389 (8)SEA FILE=PASCAL L384

L390 (2)SEA FILE=PASCAL L389 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L391 (0)SEA FILE=JICST-EPLUS L384

L392 (0)SEA FILE=JICST-EPLUS L391 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L393 (0)SEA FILE=LIFESCI L384

L394 (0)SEA FILE=LIFESCI L393 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L395 (1)SEA FILE=CANCERLIT L384

L396 (1)SEA FILE=CANCERLIT L395 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L397 (11)SEA FILE=DRUGU L384

L398 (11)SEA FILE=DRUGU L397 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L399 (0)SEA FILE=VETU L384

L400 (0)SEA FILE=VETU L399 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L401 (0)SEA FILE=VETB L384

L402 (0)SEA FILE=VETB L401 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L403 (7)SEA FILE=SCISEARCH L384

L404 (3)SEA FILE=SCISEARCH L403 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L405 (44)SEA L384 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR
LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L406 (3)SEA FILE=BIOSIS L380

L407 (28)SEA FILE=BIOSIS L406 OR L386

L408 (0)SEA FILE=TOXCENTER L380

L409 (2)SEA FILE=TOXCENTER L408 OR L388

L410 (0)SEA FILE=PASCAL L380

L411 (2)SEA FILE=PASCAL L410 OR L390

L412 (0)SEA FILE=JICST-EPLUS L380

L413 (0)SEA FILE=JICST-EPLUS L412 OR L392

L414 (0)SEA FILE=LIFESCI L380

L415 (0)SEA FILE=LIFESCI L414 OR L394

L416 (0)SEA FILE=CANCERLIT L380

L417 (1)SEA FILE=CANCERLIT L416 OR L396

L418 (3)SEA FILE=DRUGU L380

L419 (12)SEA FILE=DRUGU L418 OR L398

L420 (0)SEA FILE=VETU L380

L421 (0)SEA FILE=VETU L420 OR L400

L422 (0)SEA FILE=VETB L380

L423 (0)SEA FILE=VETB L422 OR L402

L424 (0)SEA FILE=SCISEARCH L380

L425 (3)SEA FILE=SCISEARCH L424 OR L404
L426 (48)SEA L380 OR L405
L427 (9)SEA FILE=BIOSIS L407 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L428 (0)SEA FILE=TOXCENTER L409 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L429 (0)SEA FILE=PASCAL L411 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L430 (0)SEA FILE=JICST-EPLUS L413 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L431 (0)SEA FILE=LIFESCI L415 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L432 (1)SEA FILE=CANCERLIT L417 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L433 (7)SEA FILE=DRUGU L419 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L434 (0)SEA FILE=VETU L421 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L435 (0)SEA FILE=VETB L423 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L436 (1)SEA FILE=SCISEARCH L425 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L437 (18)SEA L426 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L438 (3)SEA FILE=BIOSIS L380
L439 (0)SEA FILE=BIOSIS L427 AND L438
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L476(0)SEA FILE=VETB L475 NOT L455
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PROCESSING COMPLETED FOR L222
PROCESSING COMPLETED FOR L255
PROCESSING COMPLETED FOR L479

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ANSWERS '3-5' FROM FILE WPIX
ANSWER '6' FROM FILE MEDLINE
ANSWER '7' FROM FILE EMBASE
ANSWERS '8-10' FROM FILE BIOSIS
ANSWERS '11-12' FROM FILE DRUGU

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CONTINUE? (Y)/N:y

L639 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:407352 HCAPLUS

DOCUMENT NUMBER: 142:457415

TITLE: Contribution of mitogen-activated protein kinases to
NMDA-induced neurotoxicity in the rat retina

AUTHOR(S): Munemasa, Yasunari; Ohtani-kaneko, Ritsuko; Kitaoka,
Yasushi; Kuribayashi, Kohei; Isenoumi, Kazuyuki; Kogo,
Jiro; Yamashita, Kayoko; Kumai, Toshio; Kobayashi,
Shinichi; Hirata, Kazuaki; Ueno, Satoki

CORPORATE SOURCE: Department of Ophthalmology, Saint Marianna University
School of Medicine, Miyamae-ku, Kawasaki-shi,
Kanagawa, 216-8511, Japan

SOURCE: Brain Research (2005), 1044(2), 227-240
CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 13 May 2005

AB We examined the contributions of the mitogen-activated protein kinases
(MAPKs) family [extracellular signal-regulated kinase (ERK), p38 kinase
(p38), and **c-Jun N-terminal**
kinase (JNK)] to N-methyl-D-aspartate (NMDA)-induced neurotoxicity
in the rat retina. Detection of apoptotic cell death in the retinal
ganglion cell layer (RGCL) and the inner nuclear layer (INL) by terminal
deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling
(TUNEL) staining began 6 h after intravitreal NMDA (100 nmol) injection
and continued to increase thereafter. Western blot anal. showed that
phosphorylated MAPKs (p-MAPKs) were expressed in the retina following a
temporal manner: maximal expression of phosphorylated ERK (p-ERK) at 1 h,
maximal expression of phosphorylated p38 (p-p38) at 6 h, and beginning of
phosphorylated JNK (p-JNK) significant increase at 6 h after injection.
An immunohistochem./TUNEL co-localization study showed that p-JNK- and
p-p38-pos. cells in the RGCL were frequently TUNEL-pos., whereas few
p-ERK-pos. cells were TUNEL-pos. Moreover, co-injection of inhibitors for
JNK (0.2 nmol **SP 600125**) and/or p38 (2.0 nmol **SB**
203580) with NMDA was effective in ameliorating NMDA-induced apoptotic
cell loss in the RGCL 12 h after injection, as shown by TUNEL-pos. cell
counts. These inhibitors also protected the inner retina as shown by
morphometric studies such as cell counts in the RGCL and measurement of
the inner plexiform layer (IPL) thickness 7 days after injection. On the
other hand, an ERK inhibitor (2.0 nmol **U 0126**) did not suppress
NMDA-induced cell death in the RGCL nor thinning of the IPL. These
findings suggest that JNK and p38 are proapoptotic in NMDA-induced cell
death in the RGCL, but not ERK.

CC 2-8 (Mammalian Hormones)

Section cross-reference(s): 4

IT **Eye**

(ganglion cell; MAP kinase contribution to NMDA-induced neurotoxicity
in retina of rats)

IT **Eye**

(retina; MAP kinase contribution to NMDA-induced neurotoxicity in
retina of rats)

IT 137632-07-6, Protein kinase ERK1 137632-08-7, Protein kinase ERK2
155215-87-5, **c-Jun N-terminal**

kinase 165245-96-5, p38 MAP kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(MAP kinase contribution to NMDA-induced neurotoxicity in retina of rats)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Ambati, J	1997	115	1161	Arch Ophthalmol	MEDLINE
Barber, A	2003	27	283	Prog Neuro-Psychopa	HCAPLUS
Chen, T	2001	904	177	Brain Res	HCAPLUS
Choi, D	1988	1	623	Neuron	MEDLINE
Chun, M	2000	868	358	Brain Res	HCAPLUS
Deng, J	2000	16	199	Yanke Xuebao	HCAPLUS
Derijard, B	1995	267	682	Science	HCAPLUS
Freshney, N	1994	78	1039	Cell	HCAPLUS
Han, J	1994	265	808	Science	HCAPLUS
Harper, S	2001	13	299	Cell Signalling	HCAPLUS
Harris, C	2002	83	992	J Neurosci	HCAPLUS
Hayashi, A	1997	38	372	Invest Ophthalmol Vi	MEDLINE
Honjo, M	2000	42	552	Invest Ophthalmol Vi	
Irving, E	2000	857	71	Brain Res	
Irving, E	2002	23	631	J Cereb Flow Metab	
Jiang, Q	2002	956	194	Brain Res	HCAPLUS
Ju, W	1999	10	419	NeuroReport	HCAPLUS
Kawasaki, H	1997	272	18518	J Biol Chem	HCAPLUS
Kikuchi, M	2000	20	5037	J Neurosci	HCAPLUS
Kinkl, N	2001	276	43871	J Biol Chem	HCAPLUS
Kitaoka, Y	2003	977	46	Brain Res	HCAPLUS
Kitaoka, Y	2004	131	8	Mol Brain Res	HCAPLUS
Ko, H	1998	71	1390	J Neurochem	HCAPLUS
Labbich, A	2001	91	34	Mol Brain Res	
Lam, T	1999	40	2391	Invest Ophthalmol Vi	MEDLINE
Levy, D	1990	40	852	Neurology	MEDLINE
Li, Y	2002	15	341	Mol Vision	
Liu, C	1998	18	1337	J Neurosci	HCAPLUS
Lucas, D	1957	58	193	Arch Ophthalmol	MEDLINE
Manabe, S	2003	44	385	Invest Ophthalmol Vi	
Matini, P	1997	146	419	Exp Neurol	HCAPLUS
Miyashiro, M	1998	236	295	Graefe's Arch Clin E	HCAPLUS
Mori, T	2002	22	444	J Cereb Flow Metab	HCAPLUS
Namura, S	1998	95	4138	Proc Natl Acad Sci	
Nicole, O	2001	21	3024	J Neurosci	HCAPLUS
Peng, J	2004	279	32626	J Biol Chem	HCAPLUS
Raingaud, J	1995	270	7420	J Biol Chem	HCAPLUS
Rhee, K	2004	24	9779	J Neurosci	HCAPLUS
Roth, S	2003	44	5383	Invest Ophthalmol Vi	
Schwarzschild, M	1997	17	3455	J Neurosci	HCAPLUS
Shanley, L	2001	21	1	J Neurosci	
Siliprandi, R	1992	8	567	Vis Neurosci	MEDLINE
Vecino, E	1999	10	1103	NeuroReport	HCAPLUS
Walton, K	1998	70	1764	J Neurochem	HCAPLUS
Wang, X	2003	86	351	J Neurochem	HCAPLUS
Xia, Z	1995	270	1326	Science	HCAPLUS
Xie, Z	2004	45	170	Glia	
Yoles, E	1998	116	906	Arch Ophthalmol	HCAPLUS
Zhang, C	2002	43	3059	Invest Ophthalmol Vi	
Zou, W	2002	67	837	J Neurosci Res	HCAPLUS

L639 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:577867 HCAPLUS
 DOCUMENT NUMBER: 141:134412
 TITLE: Lens Major Intrinsic Protein (MIP)/Aquaporin 0
 Expression in Rat Lens Epithelia Explants Requires
 Fibroblast Growth Factor-induced ERK and JNK Signaling
 AUTHOR(S): Golestaneh, Nady; Fan, Jianguo; Fariss, Robert N.; Lo,
 Woo-Kuen; Zelenka, Peggy S.; Chepelinsky, Ana B.
 CORPORATE SOURCE: Laboratory of Molecular and Developmental Biology,
 National Institutes of Health, Bethesda, MD, 20892,
 USA
 SOURCE: Journal of Biological Chemistry (2004), 279(30),
 31813-31822
 CODEN: JBCHA3; ISSN: 0021-9258
 PUBLISHER: American Society for Biochemistry and Molecular
 Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English

ED Entered STN: 20 Jul 2004

AB Lens major intrinsic protein (MIP), exclusive to the vertebrate lens, otherwise known as MIP26 and Aquaporin 0, is abundantly expressed as a lens fiber membrane protein. Although relatively less efficient compared with other aquaporins, MIP is suggested to function as a water channel, as an adhesion mol., and is required for lens transparency. Because MIP is specifically expressed in lens fiber cells, we investigated in this study the activation of MIP expression after triggering differentiation of rat lens epithelia explants by fibroblast growth factor (FGF)-2. Here, we show that MIP expression in the lens cells is regulated by FGF-2. Using Real time PCR we demonstrate that endogenous MIP levels in the explants were up-regulated upon FGF-2 stimulation, in a concentration-dependent manner. Up-regulation of MIP at the transcriptional level was simultaneous with the activation of the FGF down-stream signaling components, ERK1/2 and JNK. Specific inhibitors, UO 126 for ERK1/2 and SP 600125 for JNK, abrogated MIP expression in response to FGF-2 in the explants. This inhibition pattern was recapitulated in reporter assays for transfection of the rat lens epithelia explants, driven by the MIP promoter (-1648/+44). Our studies show that ERK1/2 and JNK signaling pathways are required for MIP expression in lens epithelia explants induced to differentiate by FGF-2.

CC 2-5 (Mammalian Hormones)

IT Eye

(lens, epithelium; lens major intrinsic protein expression in rat lens epithelia explants requires FGF-induced ERK and JNK signaling)

IT Eye

(lens, fiber cell; lens major intrinsic protein expression in rat lens epithelia explants requires FGF-induced ERK and JNK signaling)

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Belecky-Adams, T	2002	129	3795	Development	HCAPLUS
Berry, V	2000	25	15	Nat Genet	HCAPLUS
Boilly, B	2000	11	295	Cytokine Growth Fact	HCAPLUS
Boyle, D	1999	68	41	Exp Eye Res	HCAPLUS
Cadena, D	1992	6	2332	FASEB J	HCAPLUS
Chamberlain, C	1989	1	125	Growth Factors	MEDLINE
Chepelinsky, A	2003	300	41	J Exp Zool Part A Co	
Chow, R	1995	121	4383	Development	HCAPLUS
Depianto, D	2003	9	288	Mol Vis	HCAPLUS
Dunia, I	1998	111	2109	J Cell Sci	
Egwuagu, C	1994	166	557	Dev Biol	HCAPLUS

Faber, S	2002	129	3727	Development	HCAPLUS
Fan, J	2004	45	863	Investig Ophthalmol	
Fotiadis, D	2000	300	779	J Mol Biol	HCAPLUS
Francis, P	2000	9	2329	Hum Mol Genet	HCAPLUS
Gong, X	2001	42	539	Investig Ophthalmol	MEDLINE
Grey, A	2003	77	567	Exp Eye Res	HCAPLUS
Klok, E	1998	67	425	Exp Eye Res	HCAPLUS
Kok, A	2002	20	27	Growth Factors	HCAPLUS
Lang, R	1999	40	3075	Investig Ophthalmol	MEDLINE
Le, A	2001	233	394	Dev Biol	HCAPLUS
Leenders, W	1997	67	193	Mech Dev	HCAPLUS
Lovicu, F	1998	125	3365	Development	HCAPLUS
Lovicu, F	2001	128	5075	Development	HCAPLUS
McAvoy, J	1989	107	221	Development	HCAPLUS
McAvoy, J	1999	13	425	Eye	
Michea, L	1995	61	293	Exp Eye Res	HCAPLUS
Mulders, S	1995	270	9010	J Biol Chem	HCAPLUS
Ochi, H	2003	278	537	J Biol Chem	HCAPLUS
Ohtaka-Maruyama, C	1998	202	125	Dev Biol	HCAPLUS
Okamura, T	2003	81	361	Genomics	HCAPLUS
Potts, J	1998	204	277	Dev Biol	HCAPLUS
Robinson, M	1998	198	13	Dev Biol	HCAPLUS
Robinson, M	1995	121	3959	Development	HCAPLUS
Saika, S	2001	72	679	Exp Eye Res	HCAPLUS
Sax, C	1995	61	125	Exp Eye Res	HCAPLUS
Seth, R	2001	42	3239	Investig Ophthalmol	MEDLINE
Shiels, A	2000	14	2207	FASEB J	HCAPLUS
Shiels, A	2001	7	179	Physiol Genomics	HCAPLUS
Sidjanin, D	2001	74	313	Genomics	HCAPLUS
Steven, Z	2002	75	177	Exp Eye Res	
Stolen, C	2000	217	205	Dev Biol	HCAPLUS
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Varadaraj, K	1999	170	191	J Membr Biol	HCAPLUS
Verkman, A	2003	76	137	Exp Eye Res	HCAPLUS
Wride, M	2000	5	203	Apoptosis	MEDLINE
Wride, M	1996	61	77	Differentiation	HCAPLUS
Yu, X	2004	117	871	J Cell Sci	HCAPLUS
Zatechka, S	2002	74	703	Exp Eye Res	

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L639 ANSWER 3 OF 12 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-591917 [60] WPIX

DOC. NO. CPI: C2005-178393

TITLE: Increasing Th2 cytokine levels useful for reducing inflammation, comprises providing inhibitor of Itchy homolog E3 ubiquitin protein ligase or kinase inhibitor (mitogen-activated protein kinase kinase kinase 1 or c-Jun N-terminal kinase 1).

DERWENT CLASS: B04 D16

INVENTOR(S): GAO, M; KARIN, M; LABUDA, T

PATENT ASSIGNEE(S): (REGC) UNIV CALIFORNIA

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005079458	A2	20050901	(200560)*	EN	103	A61K000-00	
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ZM ZW							
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DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005079458	A2	WO 2005-US5066	20050217

PRIORITY APPLN. INFO: US 2004-546540P 20040219
 INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2005079458 A UPAB: 20050920

NOVELTY - Increasing (M1) Th2 cytokine levels produced by T cells comprises providing (i) an inhibitor of ITCH or a kinase inhibitor, where the kinase is mitogen-activated protein kinase kinase kinase 1 (MEKK1) or c-Jun N-terminal kinase 1 (JNK1), (ii) T cells, and (iii) test agent.

DETAILED DESCRIPTION - Increasing (M1) Th2 cytokine levels produced by T cells comprises:

(a) providing (i) an inhibitor of ITCH or a kinase inhibitor, where the kinase is MEKK1 or JNK1, (ii) T cells, and (iii) test agent;

(b) contacting the T cells in the presence of the test agent to produce contacted T cells and in the absence of the test agent to produce control T cells; and

(c) detecting reduced activity of ITCH in the contacted T cells compared to ITCH or to the kinase in the control T cells, where the detecting identifies the test agent as increasing Th2 cytokine levels produced by T cells.

INDEPENDENT CLAIMS are also included for:

(1) identifying (M2) a test agent as reducing the level of differentiation of T cells into TH1 cells;

(2) inflammation (M3) and disease associated with TH1 cell abundance by increasing the in vivo production of Th2 cells;

(3) a composition comprising a transgenic mouse that comprises MEKK1-/MEKK1- or MEKK1-/MEKK1+;

(4) identifying (M4) therapeutic agents that are useful in reducing one or more of MEKK-MEKK4/MKK7-JNK-ITCH cascade pathway activity and direct MEKK1-ITCH protein to protein interactions; and

(5) a method where the JNK inhibitor comprises SP600125.

ACTIVITY - Antiinflammatory; Neuroprotective; Antidiabetic; Antithyroid; Antirheumatic; Antiarthritic; Immunomodulator.

No biological data given.

MECHANISM OF ACTION - Protein kinase inhibitor.; ITCH inhibitor; Itchy homolog E3 ubiquitin protein ligase inhibitor; MEKK-1 protein kinase inhibitor; Jun N terminal kinase inhibitor; MEKK-4 protein kinase inhibitor; MKK-7 alpha protein kinase inhibitor; Antisense oligonucleotide inhibitor; RNAi; RNA interference.

USE - The method is useful for increasing Th2 cytokine levels produced by T cells. Especially the method is useful for reducing

inflammation and disease, where the disease is multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, or rheumatoid arthritis.

Dwg.0/18

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-F04; B04-G02; B04-G03; B04-L04C; B04-L08;
B04-M01; B04-N02; B04-P0100E; B06-D18; B11-C08E3;
B11-C08E7; B12-K04E1; B14-C03; B14-C09B; B14-D06C;
B14-D10; B14-G02D; B14-G03; B14-N11; B14-S01;
B14-S03B; B14-S03C; B14-S04; D05-A02B; D05-A02F;
D05-H09; D05-H11; D05-H16A

TECH UPTX: 20050920

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The method of (M1) further comprises identifying the test agent as increasing the level of one or more of Th2 cytokine or identifying the test agent as decreasing the level of TH1 cytokines. The kinase inhibitor preferably comprises SB600125.

Alternatively, the method comprises providing (i) T cells and (ii) agent that reduces activity of an ITCH or agent that reduces activity of a kinase, where the kinase is MEKK1 or JNK 1, and contacting the T cells with the agent where the agent reduces the activity of the ITCH or of the kinase.

The method further comprises identifying the test agent as increasing the level of IL-10 produced by the T cells. The T cells are inflammatory disease T cells.

Increasing Th2 cytokine levels produced by T cells comprises reducing the activity of an ITCH, of a MEKK1, or of a JNK1. Specifically, increasing Th2 cytokine levels produced by pro-inflammatory disease T cells comprises providing (i) pro-inflammatory disease T cells, and (ii) agent that reduces activity of an ITCH, and contacting the pro-inflammatory disease T cells with the agent under conditions such that the agent increases the level of interleukin (IL)-10 produced by the T cells.

In (M2) the method comprises reducing MEKK1 catalytic activity in the T cells. Reduction of the MEKK1 catalytic activity comprises increasing the level of differentiation of the T cells into Th2 cells. Reducing of the MEKK1 catalytic activity comprises increasing the level of one or more Th2 cell cytokine that is produced by the T cells, where the increased level of the Th2 cytokine occurs in the absence of an increase in the level of one or more TH1 cytokine, where the TH1 cytokine is interferon-gamma or IL-2. The Th2 cytokine is IL-4, IL-5, IL-10, or IL-13. Increasing the level of the Th2 cell cytokine comprises increasing the level of mRNA encoding the Th2 cytokine, where the mRNA encoding the Th2 cytokine is increased 5-fold. Reducing of the MEKK1 catalytic activity comprises increasing the level of proliferation of Th2 cells that differentiate from the T cells. Reducing of the MEKK1 catalytic activity comprises introducing a mutation in the gene encoding MEKK1. The T cells comprise thymocyte cells or splenocyte cells. The T cells are in vitro or are in vivo in an animal, where the animal is human. The human is suspected or is not suspected of having a TH1-mediated disease, or suspected of being capable or not capable of developing a TH1-mediated disease. The method comprises one or more of: identifying the agent as increasing the level of differentiation of the T cells into Th2 cells, identifying the agent as increasing the level of one or more Th2 cell cytokine that is produced by the T cell, or identifying the agent as increasing the level of proliferation of Th2 cells that differentiate from the T cells.

Alternatively, the method comprises providing a test agent and MEKK1, contacting the test agent and the MEKK1, and detecting reduced MEKK1 kinase activity in the presence of the agent compared to in the absence of the agent, thus identifying the test agent as causing one or more of increasing Th2 cells, decreasing the level of TH1 cells, and decreasing

TH1 disease.

The method of (M3) comprises reducing one or more of MEKK1-MEKK4/MKK7-JNK-ITCH cascade pathway activity and direct MEKK1-ITCH protein to protein interactions, where the disease is multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, or rheumatoid arthritis.

Reducing comprises using one or more MEKK1 enzyme inhibitors, where the enzyme inhibitors comprise SP600125. Reducing comprises using one or more neutralizing antibodies that specifically bind to MEKK1. Reducing is achieved by reducing expression of the MEKK1 gene.

Reducing comprises using one or more MEKK4/MKK7 enzyme inhibitors, where the MEKK4/MKK7 enzyme inhibitors comprise SP600125. Reducing comprises neutralizing antibodies that specifically bind to MEKK4/MKK7. Reducing comprises inhibiting expression of the MEKK4/MKK7 gene.

Reducing comprises using ITCH enzyme inhibitors. Reducing comprises using neutralizing antibodies that specifically bind to ITCH. Reducing comprises inhibiting the expression of the ITCH gene.

The expression of a JNK, MEKK1, MEKK4/MKK7, or ITCH gene is suppressed by the use of one or more of RNAi, and antisense molecules. The neutralizing antibody is chosen from human antibody and humanized antibody that invoke minimum and therapeutically acceptable level of immunogenic defense response in a human. The MEKK1-ITCH interactions are reduced by using SP600125.

The MEKK1-ITCH interactions are reduced by the use of neutralizing antibodies against one or more of MEK, K1 and ITCH.

(M4) comprises providing (i) WT and MEKK1KD thymocytes stimulated with, (ii) anti-CD3, (iii) anti-CD28 for 24 hrs, and (iv) in the absence or presence (0.5 mM) cfa JNK inhibitor, preparing cell lysates from the thymocytes, immunoblotting the lysates, and determining levels of one or more of ITCH, c-Jun and JunB to identify therapeutic agents that are useful in reducing cascade pathway activity.

L639 ANSWER 4 OF 12 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-273043 [28] WPIX

CROSS REFERENCE: 2003-712583 [67]

DOC. NO. CPI: C2005-085327

TITLE: New conjugates of biologically active compounds for treating e.g. inflammatory disorders, infectious diseases, cancer, allergy and immune disorders, contain a transportophore, a bond or linker and a non-antibiotic therapeutic agent.

DERWENT CLASS: B02 B03

INVENTOR(S): BECK, A; BURNET, M; EGGERS, M; FLOHR, C; GUSE, J; GUTKE, H; KHOBZAQI, M; MARGUTTI, S

PATENT ASSIGNEE(S): (SYNO-N) SYNOVO GMBH

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005027828	A2	20050331	(200528)*	EN	97	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
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KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005027828	A2	WO 2004-US26485	20040816

PRIORITY APPLN. INFO: US 2003-644600 20030820

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2005027828 A UPAB: 20050504

NOVELTY - Conjugates of biologically active compounds are new and contain a transportophore, a bond or linker and a non-antibiotic therapeutic agent.

DETAILED DESCRIPTION - A conjugate compound (I) of biologically active compounds is new. The compound is of formula T-(L-C)m.

T = transportophore;

L = a bond or a linker having a molecular weight up to 240 dalton;

C = a non-antibiotic therapeutic agent; and

m = 1-8;

The transportophore has an immune selectivity ratio of at least 2 and is covalently bonded to the non-antibiotic therapeutic agent via the bond or the linker. The compound has an immune selectivity ratio of at least 2.

ACTIVITY - Antiinflammatory; Antimicrobial; Cytostatic; Antiallergic; Immunomodulator; Vasotropic; Cardiovascular-Gen.; Respiratory-Gen.; Dermatological; Antirheumatic; Hepatotropic.

MECHANISM OF ACTION - Protein kinase inhibitor; Protease inhibitor.

USE - (I) is useful to treat an inflammatory disorder, infectious disease, cancer, allergy or immune disorder (claimed). (I) is also useful to treat diseases such as metabolic cardiovascular, pulmonary, dermatological, rheumatological and hepatic diseases.

ADVANTAGE - (I) improves the ease of formulation, gastric stability, bioavailability, stability, disposition, elimination, half life, efficacy, safety, duration of action and selectivity of the agent. (I) has:

- (a) improved uptake across the intestinal, jejunal, duodenal, colonic, or other mucosa;
- (b) reduced first pass effect by mucosal oxygenases;
- (c) reduced or altered detoxification by degradative enzymes of the body;
- (d) reduced efflux;
- (e) selective accumulation of the therapeutic agent in one or more immune, fibroblast, hepatic, renal, glial, or other target cells;
- (f) potential for hydrolytic or other forms of separation on a timescale compatible with therapy and the other desired disposition events;
- (g) enhanced pharmacological effect in the target cells through greater concentration, sustained release, reduced substrate competition effect or other mechanisms;
- (h) reduced or modified dose;
- (i) modified route of administration;
- (j) reduced or altered side effects;
- (k) alternative uses; and
- (l) alternative formulations.

Tests details are described but no results given.

Dwg.0/2

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B07-H; B10-A06; B10-A08; B10-A09B; B10-A11B;
 B10-A15; B10-A16; B10-A17; B10-A18; B10-B01;
 B10-B02; B10-B03; B10-B04; B10-C04; B10-D03;
 B10-E04; B10-F02; B10-G02; B14-A01; B14-A02;

B14-C01; B14-C03; B14-C06; B14-D02A2; B14-D05D;
 B14-D06C; B14-D07C; B14-F01; B14-F02; B14-F03;
 B14-F04; B14-F06; B14-G02; B14-G02A; B14-G03;
 B14-H01; B14-K01; B14-N17; B14-S13

TECH

UPTX: 20050504

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises reaction of a transportophore having a reactive moiety with a therapeutic agent having another reactive moiety. One of the two reactive moieties is a leaving group (e.g. -Cl or OR) and the other is a derivatizable group (e.g. -OH or -NH-). The transporter is covalently bonded to the therapeutic agent via a reaction between the two reactive moieties. When a linker is present, each of the two reactive moieties, is a leaving group or a derivatizable group and each reacts with its reactive counterpart in the linker to form a covalent bond.

Preferred Components: The transportophore is an amphiphilic molecule (having a pKa value of 6.5-9.5) or a cyclic or heterocyclic molecule (preferably a cyclic or heterocyclic molecule having an attached sugar, a macrolactone or macroether having an attached sugar, or a macrolide (mono-, di or tri basic) or a ketolide having an amino sugar).

Preferably, (I) is a macrolide of formula (Ia)-(Id).

In (Ia):

X = N(R7)-CH₂, CH₂-N(R7), C(=O), C(=NOR8), CH(OR9), CH(NR10R11),

C(=NR12), OC(=O) or C(=O)O;

Y = independently linker;

Z = C(=O), CH(R16); either

R1 = H, CH₃, 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkenyl, 6-10C aryl-(1-5C alkyl), 2-9C heteroaryl-(1-5C alkyl), (1-4C alkyliden)-NR18R19, Y-R13, C(=O)-Y-R15 or C(=O)-R15;

R2 = H, (1',2'-cis)-OH, (1',2'-trans)-OH, (1',2'-cis)-OR15, (1',2'-trans)-OR15, (1',2'-cis)-SH or (1',2'-cis)-S-Y-R13, (R1 and R2 are connected via a OC(=O)CHR16);

R3, R4 = H, C(=O)-Y-R15 or C(=O)-R15; either

R5 = H; or

R4+R5 = Z;

R6 = H or CH₃;

R7 = H, CH₃, Y-R13, C(=O)-Y-R15 or C(=O)-R15;

T = 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl) (where alkyl, alkenyl, alkynyl, aryl or heteroaryl optionally substituted by 1-5 substituents of halo, 1-4C alkyl, 1-4C alkenyl, 1-4C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, 1-4C alkoxy, OH, NO₂, CN, azido, mercapto, R18R19, R18C(=O), R18C(=O)O, R18OC(=O)O, R18NHC(=O), R18C(=O)NH, R18R19NC(=O) or R18OC(=O));

R8 = T, H, Y-R13, R13, C(=O)-R17 or (1-4C alkyliden)-NR18R19;

R9 = T or H;

T1 = 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl) or (1-4C alkyliden)-NR18R19;

R10 = T1 or H;

R11 = T1, H, Y-R13, C(=O)-Y-R15 or C(=O)-R15;

R12 = T1, H or Y-R13;

R13, R15 = therapeutic agent;

R16 = H, CH₃, 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, (1-8C)(1-4C alkoxy) alkyl, (1-8C)(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl), (1-4C alkyliden)-NR18R19 or Y-R13;

R17 = O-R20-aryl (optionally substituted by -(X-a)-Y therapeutic agent;

X-a = therapeutic agent (S, O or NH);

R18, R19 = H, 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl) or

(2-9C heteroaryl)-(1-5C alkyl); and
R20 = Halo, 1-3C alkyl, NO₂, CN, OCH₃, N(CH₃)₂, N₃, SH or S(1-4C alkyl).
In (Ib):
R1 = 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkenyl, 6-10C aryl-(1-5C alkyl), 2-9C heteroaryl-(1-5C alkyl), S(=O)_k(1-10C alkyl), S(=O)_k(1-10C alkenyl), S(=O)_k(1-10C alkynyl), S(=O)_k(6-10C aryl), S(=O)_k(2-9C heteroaryl), cycloalkyl, heterocycloalkyl (optionally be substituted by 1-3 halo, CN, OH, 1-4C alkyloxy, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, NR18R19, R18C(=O), R18C(O)O, R18OC(=O), R18C(=O)NH, R18NHC(=O), R18R19NC(=O) or R18OC(=O)), H, CH₃, (1-4C alkyliden)-NR18R19, Y-R13, C(=O)-Y-R15, C(=O)-R15, S(=O)_k-Y-R15 or S(=O)_k-R15;
k = 0-2;
R-3a, R-3b = H, R1, OH, OR11 or NR10R11;
R8 = H, Y-R13 or C(=O)-R17;
R9 = H, 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl) or (2-9C heteroaryl)-(1-5C alkyl); either
R10, R11 = H, 1-10C alkyl, 1-10C alkenyl, 3-10C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 2-9C heteroaryl (optionally substituted by 1-3 halo, CN, OH, 1-4C alkyloxy, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, NR18R19, R18C(=O), R18C(O)O, R18OC(=O), R18C(O)NH, R18NHC(=O), R18R19NC(=O) or R18OC(=O)-O); or
R10 = H; and
R11 = Y-R13, C(=O)-Y-R15, C(=O)-R15, S(=O)_k(1-10C alkyl), S(=O)_k(1-10C alkenyl), S(=O)_k(1-10C alkynyl), S(=O)_k(6-10C aryl), S(=O)_k(2-9C heteroaryl), S(=O)_k-Y-R15, S(=O)_k-R15, where k is 0-2 and alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl (all optionally substituted).
In (Ic):
X = N(R9)-CH₂, CH₂-N(R9), C(=O), C(=NOR10), C(OR11)H, CH(NR12R13), C(=NR14), OC(=O) or C(=O)O;
Y = linker; either
R1 = OR17 or NR17R18; or
R1+OR4, R1OR5 = lactone; or
R1+R2 = lactone or lactam;
T2 = halo, 1-4C alkyl, 1-4C alkenyl, 1-4C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, 1-4C alkoxy, OH, NO₂, CN, azido, mercapto, R20R21N, R20C(=O), R20C(=O)O, R20OC(=O), R20NHC(=O), R20C(=O)NH, R20R21NC(O) or R20OC(=O)O, Y-therapeutic agent or therapeutic agent;
R2 = O-2-cladinosyl, H, X-a, azido, NO₂, CN, OR17, OR22, NR17R18, SR17 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);
X-a = halo;
R3 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);
R4 = O-2-desosaminyl, H, C(=O)R17, Y-therapeutic agent, therapeutic agent, S(=O)₂R17 (Provided that R17 is not H), C(=O)NR17R18(1-6C alkyl), 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl or 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), where R4 is connected to R2 containing a N or O by -C(=O), -S(=O)_n, -CR20R17, -CR20 (therapeutic agent) forming in

dependence of R2 or 6 or 7 membered ring;

n = 1-2;

R5 = R20 or C(=O)R20, where R4 and R5 is connected by C(=O), -S(=O)n, -CR20R17, -CR20 (therapeutic agent);

R6, R7, R8 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), -C(=O)R17, Y-therapeutic agent, -therapeutic agent, -S(=O)2R17 (provided that R17 is not H) or -C(=O)NR17R18, two of each R6, R7, R8 are connected by C(=O), -S(=O)n, -CR20R17, -CR20 (therapeutic agent);

R9 = H, CH3, Y-therapeutic agent, therapeutic agent, 1-6C alkyl, 1-6C alkenyl or 1-6C alkynyl (where alkyl, alkenyl, alkynyl are all optionally substituted by 1-5 substituents of T2);

R10 = C(=O)-aryl, therapeutic agent, H, 1-6C alkyl, 1-6C alkenyl or 1-6C alkynyl (where alkyl, alkenyl, alkynyl are optionally substituted by 1-5 substituents of T2);

R11 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl (where alkyl, alkenyl, alkynyl are optionally substituted by 1-5 substituents of T2) or -C(=O)R17;

R12, R13 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), -C(=O)R17, S(=O)2R17 (provided that R17 is not H) or -C(=O)NR17R18;

R14, R17, R18 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);

R20, R21 = H or 1-6C alkyl; and

R22 = C(=O)R17, Y-therapeutic agent, therapeutic agent, S(=O)2R17 providing R17 is not H, or -C(=O)NR17R18.

Provided that connected to a N, R17, R18 may form a cyclic structure of 4-7 members (including the nitrogen).

In (Id):

m = 0-3;

n = 0-7;

X = O, S, Se, NR1 or PR1 (provided that at least one X is NR1);

A = CH2, CHR2, CR2R3 or C(=O) (provided that at least one X is -NR1- is not an amide);

k = 0-2;

R1 = H, 1-10C alkyl, optionally substituted by F, CN, R4, R4O2C, R4C(=O)NH or R4S(=O)k, R4C(=O) or R4S(=O)k;

R2, R3 = NH2, NHR1, NR1R5, OH, OR4, R4C(=O)(1-6C alkyl), 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl(1-6C alkyl), 2-9C heterocycloalkyl(1-6C alkyl), 6-10C aryl(1-6C alkyl) or 2-9C heteroaryl(1-6C alkyl), where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substitutes of T3;

T3 = halo, 1-4C alkoxy, OH, nitro, CN, -C(=O)-OR8, -C(O)N(H)R8, 6-10C aryl, 2-9C heteroaryl, NasteriskR5R6R7 wherein asterisk is no or a positive charge, one or two of R2, R3 can be a directly coupled therapeutic agent;

R4 = NH2, NHR9, NR9R5, OH, OR9, 1-6C alkyl, 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl(1-6C alkyl), 2-9C heterocycloalkyl(1-6C alkyl), 6-10C aryl(1-6C alkyl) or 2-9C heteroaryl(1-6C alkyl), (where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substituents of T3);

R5, R6 = H, 1-6C optionally substituted by OH, 6-10C aryl or 2-9C heteroaryl;

R7 = lone electron pair, CH3, C2H5, C3H7 or CH2-C6H5;

R8 = therapeutic agent; and
 R9 = 1-6C alkyl, 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl(1-6C alkyl), 2-9C heterocycloalkyl(1-6C alkyl), 6-10C aryl(1-6C alkyl) or 2-9C heteroaryl(1-6C alkyl), where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substituents of T3.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compound: The non-antibiotic therapeutic agent is an anti-inflammatory agent (preferably a protein kinase inhibitor, a protease inhibitor or an 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor); an anti-infectious agent (preferably a protease inhibitor); an anti-cancer agent; a fluorescent molecule useful in diagnostic or exploratory applications; an immune-suppressant agent (preferably an analog of vitamin D or a statin); or an agent for treating a hematopoietic disorder, metabolic disease, excessive coagulation or hypercholesterolemia.

ABEX UPTX: 20050504

ADMINISTRATION - Administration of (I) is 0.1-20 mg/kg, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, subcutaneously, orally, buccally, nasally, transmucosally, topically, ocularly or by inhalation.

EXAMPLE - A solution of simvastatin (420 mg) in dichloromethane (3 ml) was treated with succinic anhydride (110 mg) and 4-(dimethylamino)pyridine (DMAP) (10 mg). After 36 hours, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (210 mg) and drug carrier of formula (2) (600 mg) was added under stirring. After 1 hour, the mixture was passed through a pad of silica gel, eluting with chloroform:isopropanol:methanolic ammonia (30:1:1) to yield macrolide of formula (4) as an off white solid (440 mg; 40% yield).

DEFINITIONS - Preferred Definitions: In (I),
 L = 1-8C alkyl, 1-8C alkenyl, 1-8C alkynyl, 3-10C cycloalkyl, 6-10C aryl, 2-9C heteroalkyl or 2-9C heteroaryl, where the alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl spacing elements are optionally substituted by 1-6C alkyl, 1-4 halogens, 1-4C alkoxy, 1-4C alkoxy carbonyl, OH, amino, 1-4C (di)alkylamino, 3-10C cycloalkyl, 1-6C alkylcarbonyloxy, 1-6C alkylcarbonylamido, 1-4C (di)alkylamio carbonyl, nitro, CN, 1-4C alkylimino, mercapto or 1-4C alkylmercapto.

L639 ANSWER 5 OF 12 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-833589 [82] WPIX

DOC. NO. CPI: C2004-289361

TITLE: Treating disease e.g., cystic fibrosis in human patient having mutation in cystic fibrosis transmembrane conductance regulator gene, involves administering peroxisome proliferator-activated receptor gamma inducer to patient.

DERWENT CLASS: B04 B05 D16

INVENTOR(S): FREEDMAN, S D

PATENT ASSIGNEE(S): (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004098510	A2	20041118	(200482)*	EN	43	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							

KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ
 OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG
 US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004098510	A2	WO 2004-US13412	20040430

PRIORITY APPLN. INFO: US 2003-466672P 20030430

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2004098510 A UPAB: 20041223

NOVELTY - Treating (M1) a disease in a human patient having a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, where the mutation is associated with the disease, involves administering peroxisome proliferator-activated receptor gamma (PPAR- gamma) inducer, PPAR- gamma agonist, AP-1 inhibitor, STAT inhibitor, nuclear factor kappa B (Nf-kappaB) inhibitor or an antioxidant to the patient.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for identifying (M2) a compound useful for treating a disease in a patient having a mutation in the CFTR gene, where the mutation is associated with the disease, involving:

(a) providing cells that express a PPAR gamma , contacting the cells with a candidate compound, and assessing the level of PPAR gamma expression in the cells relative to the level of PPAR gamma expression in the absence of the candidate compound, where the candidate compound that increases the level of PPAR gamma expression is identified as a compound useful for treating the disease;

(b) carrying out the providing and contacting steps as mentioned in (a), and assessing the half life of the PPAR gamma protein in the cells relative to the half life of the PPAR gamma protein in the absence of the candidate compound, where the candidate compound that increases the half life is identified as a compound useful for treating the disease; or

(c) carrying out the providing and contacting steps as mentioned in (a), and assessing the level of the PPAR gamma translocation to the nucleus of the cells relative to the level of PPAR gamma expression in the absence of the candidate compound, where the candidate compound that increases the level of PPAR gamma translocation to the nucleus is identified as a compound useful for treating the disease.

ACTIVITY - CNS-Gen.; Respiratory-Gen.; Antiinflammatory; Antiasthmatic; Antidiabetic.

MECHANISM OF ACTION - Inducer of PPAR- gamma ; PPAR- gamma agonist; AP-1 inhibitor; STAT inhibitor; Nf-kappaB inhibitor.

No supporting data is given.

USE - (M1) is useful for treating a disease in a human patient having a mutation in CFTR gene, where the mutation is associated with the disease chosen from cystic fibrosis, pancreatitis, chronic obstructive pulmonary disorder (COPD), asthma, chronic sinusitis, primary sclerosing cholangitis and congenital bilateral absence of the vas deferens (claimed). The PPAR gamma agonist is useful in the treatment of diabetes, and in decreasing inflammation.

DESCRIPTION OF DRAWING(S) - The figure is a bar graph representing peroxisome proliferator-activated receptor gamma mRNA expression levels in various tissues of cystic fibrosis transmembrane conductance regulator(-/-) and wild-type mice.

Dwg.1/7

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B03-A; B03-F; B03-H; B04-B03A; B04-C01A; B05-B01D;
 B05-B01P; B05-B02C; B05-C05; B06-A01; B06-D01;
 B06-D18; B07-B03; B07-D04C; B07-D12; B07-F01;
 B10-A06; B10-B01A; B10-B02D; B10-C03; B10-C04C;
 B10-C04E; B10-D03; B10-E02; B10-E03; B11-C07A;
 B11-C08; B12-K04E; B14-C03; B14-K01; B14-L01;
 B14-L06; B14-N04; B14-N13; B14-S03; B14-S04;
 B14-S08; D05-H09; D05-H17A6

TECH UPTX: 20041223

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M2), the cells are pancreatic exocrine cells, lung cells, intestinal cells, bile duct cells, macrophages or their derivatives. The PPARGamma is PPARGamma1 or PPARGamma2. In (a) of (M2), the assessing step includes Western blotting. The assessing step involves measuring the amount of PPARGamma RNA in the cells. In (c) of (M2), the assessing step includes immunohistochemistry.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: In (M1), the PPAR-gamma is a PPAR-gamma1. The PPAR inducer is substantially pure eicosapentaenoic acid. The PPAR inducer is chosen from thiazolidinediones, fluoromethyloxycarbonyl, indomethacin, ibuprofen, fenoprofen and troglitazone. The PPAR ligand is rosiglitazone. The AP-1 inhibitor is chosen from nordihydroguaiaretic acid, SP600125, SR11302, pyrrolidine dithiocarbamate, curcumin, PD98059 and spiro compounds. The STAT inhibitor is chosen from SSI-1, SSI-2 and SSI-3. The STAT inhibitor is expressed in the target cell by gene therapy. The STAT inhibitor is a tripeptide having the sequence Pro-Tyr-Leu or Ala-Tyr-Leu, where the tyrosine is phosphorylated. The NFkappaB inhibitor is chosen from 2-chloro-N-(3,5-di(trifluoromethyl) phenyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide (SP-100030), 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine (BXT-51072), declopramide (Oxi-104), dexlipotam, salicylanilide, 2-hydroxy-4-trifluoromethylbenzoic acid and 2-hydroxy-4-trifluoromethylbenzoic acid derivatives, where the 2-hydroxy-4-trifluoromethylbenzoic acid derivative is triflsal. The mutation is a deletion of Phe508. The antioxidant is a PPARGamma inducer. The antioxidant is chosen from Vitamin E, Vitamin C, S-adenosyl methionine, selenium, Vitamin C, beta-carotene, idebenone, cysteine, dithioerythritol, dithionite, dithiothreitol and pyrosulfite.

ABEX UPTX: 20041223

ADMINISTRATION - The STAT inhibitor is administered by intravenous or inhalation route (claimed). A pharmaceutical composition comprising PPARGamma inducer and a carrier is administered by oral, intramuscular, intraperitoneal, subcutaneous, intrathecal or intracerebroventricular route, at a dosage of 0.1 microg/kg-100 mg/kg, preferably 250 microg/kg-5.0 mg/kg.

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, DRUGU' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):y

L639 ANSWER 6 OF 12 MEDLINE on STN
 ACCESSION NUMBER: 2003324146 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12853963
 TITLE: JNK phosphorylates paxillin and regulates cell migration.
 AUTHOR: Huang Cai; Rajfur Zenon; Borchers Christoph; Schaller
 Michael D; Jacobson Ken

CORPORATE SOURCE: Department of Cell and Developmental Biology, Comprehensive
 Center for Inflammatory Disorders, University of North
 Carolina, Chapel Hill, North Carolina 27599-7090, USA.
 SOURCE: Nature, (2003 Jul 10) 424 (6945) 219-23.
 Journal code: 0410462. ISSN: 1476-4687.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200307
 ENTRY DATE: Entered STN: 20030711
 Last Updated on STN: 20030722
 Entered Medline: 20030721

ED Entered STN: 20030711

Last Updated on STN: 20030722

Entered Medline: 20030721

AB The c-Jun amino-terminal kinase (JNK) is generally thought to be involved
 in inflammation, proliferation and apoptosis. Accordingly, its substrates
 are transcription factors and anti-apoptotic proteins. However, JNK has
 also been shown to be required for Drosophila dorsal closure, and MAP
 kinase/ERK kinase kinase 1, an upstream kinase in the JNK pathway, has
 been shown to be essential for cell migration. Both results imply that
 JNK is important in cell migration. Here we show that JNK1 is required
 for the rapid movement of both fish keratocytes and rat bladder
 tumour epithelial cells (NBT-II). Moreover, JNK1 phosphorylates serine
 178 on paxillin, a focal adhesion adaptor, both in vitro and in intact
 cells. NBT-II cells expressing the Ser 178 --> Ala mutant of paxillin
 (Pax(S178A)) formed focal adhesions and exhibited the limited movement
 associated with such contacts in both single-cell-migration and
 wound-healing assays. In contrast, cells expressing wild-type paxillin
 moved rapidly and retained close contacts as the predominant adhesion.
 Expression of Pax(S178A) also inhibited the migration of two other cell
 lines. Thus, phosphorylation of paxillin by JNK seems essential for
 maintaining the labile adhesions required for rapid cell migration.

CT Check Tags: In Vitro

Amino Acid Sequence

Animals

Anthracenes

Cell Adhesion: PH, physiology

*Cell Adhesion Molecules: ME, metabolism

*Cell Movement: PH, physiology

Cricetulus

Cytoskeletal Proteins: GE, genetics

*Cytoskeletal Proteins: ME, metabolism

Enzyme Inhibitors

Fishes

Focal Adhesions: PH, physiology

Green Fluorescent Proteins

Hamsters

Humans

Luminescent Proteins

Mitogen-Activated Protein Kinase 8

Mitogen-Activated Protein Kinases: AI, antagonists & inhibitors

Mitogen-Activated Protein Kinases: ME, metabolism

*Mitogen-Activated Protein Kinases: PH, physiology

Molecular Sequence Data

Phosphoproteins: GE, genetics

*Phosphoproteins: ME, metabolism

Phosphorylation

Rats

Research Support, U.S. Gov't, P.H.S.

Serine: ME, metabolism

Substrate Specificity

Transfection

Tumor Cells, Cultured

RN 147336-22-9 (Green Fluorescent Proteins); 56-45-1 (Serine)
CN 0 (Anthracenes); 0 (Cell Adhesion Molecules); 0 (Cytoskeletal Proteins); 0 (Enzyme Inhibitors); 0 (Luminescent Proteins); 0 (Phosphoproteins); 0 (anthra(1,9-cd)pyrazol-6(2H)-one); 0 (paxillin); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 8); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L639 ANSWER 7 OF 12 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005359258 EMBASE

TITLE: Inflammatory responses of corneal epithelial cells to Pseudomonas aeruginosa infection.

AUTHOR: Zhang J.; Wu X.-Y.; Yu F.-S.X.

CORPORATE SOURCE: Dr. F.-S.X. Yu, Department of Cellular Biology and Anatomy, Medical College of Georgia, 1459 Laney-Walker Blvd. CB2916, Augusta, GA 30912, United States. fyu@mail.mcg.edu

SOURCE: Current Eye Research, (2005) Vol. 30, No. 7, pp. 527-534.

Refs: 32

ISSN: 0271-3683 CODEN: CEYRDM

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 004 Microbiology

012 Ophthalmology

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20050901

Last Updated on STN: 20050901

ED Entered STN: 20050901

Last Updated on STN: 20050901

AB Purpose: We hypothesized that corneal epithelium plays a role in the innate immune response by sensing the presence of pathogens and providing signals that activate the corneal defense system. We sought to determine the mechanisms involved in the activation of the signaling pathways and subsequent production of proinflammatory cytokines in human corneal epithelial cells (HCECs) in response to Pseudomonas aeruginosa infection. Methods: Epithelial monolayers of a telomerase-immortalized HCEC line, HUCL, and primary cultures of HCECs were exposed to P. aeruginosa (PA01 strain) with or without the presence of the NF- κ B inhibitor kamebakaurin, the p38 inhibitor SB203580, or the JNK inhibitor SP600125. I κ B- α phosphorylation and degradation and p38 and JNK phosphorylation were assessed at different time points by Western blot analysis. Interleukin (IL)-6, IL-8, and TNF- α levels were determined by reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA). Results: Exposure of HUCL cells and primary HCECs to P. aeruginosa resulted in rapid activation of NF- κ B as indicated by an increase in I κ B- α phosphorylation observed within 15 min and by I κ B- α degradation, which peaked in 1 hr. Two stress-activated mitogen-activated protein kinases, p38 and JNK, were also activated as their phosphorylation was induced by P. aeruginosa infection. Concomitant with the activation of these Toll-like receptor-mediated signaling pathways, transcriptional expression and subsequent secretion of IL-6 and IL-8 in HUCL cells were also induced by P. aeruginosa. Presence of the NF- κ B inhibitor kamebakaurin in culture medium blocked P.

aeruginosa-induced NF- κ B activation and inhibited IL-6, IL-8, and TNF- α expression and secretion. Inhibition of p38 or JNK also resulted in a decrease in bacteria-induced expression and secretion of these cytokines. Conclusions: *P. aeruginosa* triggers an innate immune response in HCECs, and NF- κ B and, to a lesser extent, the p38/JNK signal pathways are responsible for *P. aeruginosa*-induced proinflammatory cytokine production in these cells. Copyright .COPYRGT. Taylor & Francis Inc.

CT Medical Descriptors:

*epithelium cell
 *cornea epithelium
 *Pseudomonas aeruginosa
 *bacterial infection: DI, diagnosis
 *bacterial infection: ET, etiology
 *inflammation
 keratitis: DI, diagnosis
 immune response
 cytokine release
 cell immortalization
 reverse transcription polymerase chain reaction
 protein phosphorylation
 enzyme linked immunosorbent assay
 transcription regulation
 monolayer culture
 strain difference
 inflammatory cell
 human
 human cell
 article
 priority journal

Drug Descriptors:

*cytokine
 *toll like receptor
 anthra[1,9 cd]pyrazol 6(2h) one
 stress activated protein kinase inhibitor
 immunoglobulin enhancer binding protein
 mitogen activated protein kinase p38
 I kappa B alpha
 telomerase
 4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole
 interleukin 6
 interleukin 8
 tumor necrosis factor alpha
 glutamate dehydrogenase (NADP)
 (toll like receptor) 409141-78-2; (anthra[1,9 cd]pyrazol 6(2h) one) 129-56-6; (I kappa B alpha) 151217-48-0; (4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole) 152121-47-6; (interleukin 8) 114308-91-7; (glutamate dehydrogenase (NADP)) 9029-11-2

RN (toll like receptor) 409141-78-2; (anthra[1,9 cd]pyrazol 6(2h) one)

129-56-6; (I kappa B alpha) 151217-48-0; (4 (4 fluorophenyl) 2 (4 methylsulfinylphenyl) 5 (4 pyridyl)imidazole) 152121-47-6; (interleukin 8) 114308-91-7; (glutamate dehydrogenase (NADP)) 9029-11-2

L639 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:256352 BIOSIS

DOCUMENT NUMBER: PREV200300256352

TITLE: Defensin expression by the cornea: Multiple signalling pathways mediate IL-1beta stimulation of hBD-2 expression by human corneal epithelial cells.

AUTHOR(S): McDermott, Alison M. [Reprint Author]; Redfern, Rachel L.; Zhang, Bei; Pei, Ying; Huang, Ling; Proske, Rita J.

CORPORATE SOURCE: College of Optometry, University of Houston, 4901 Calhoun Road, 505 J. Davis Armistead Building, Houston, TX,

77204-2020, USA

amcdermott@popmail.opt.uh.edu

SOURCE: IOVS, (May 2003) Vol. 44, No. 5, pp. 1859-1865. print.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 28 May 2003

Last Updated on STN: 28 May 2003

ED Entered STN: 28 May 2003

Last Updated on STN: 28 May 2003

AB PURPOSE: To investigate the expression of human beta-defensins (hBDs) by human **corneal** epithelium and determine the effects of proinflammatory cytokines on expression of human beta-defensin (hBD)-2 by human **corneal** epithelial cells (HCECs) in culture. METHODS: RNA was extracted from **corneal** epithelial cells scraped from cadaveric **corneas** and from cultured HCECs, and RT-PCR was performed to detect hBD-1, -2, and -3 mRNA. To study the effects of proinflammatory cytokines on expression of defensin, HCECs were cultured and then exposed to interleukin (IL)-1beta or tumor necrosis factor (TNF)-alpha for up to 36 hours, with a range of concentrations (0.01-100 ng/mL). In some experiments, cells were pretreated with various cell signaling pathway inhibitors before the addition of IL-1beta. At the end of the incubations, the cells were harvested for RT-PCR and the culture media collected for the detection by immunoblot analysis of secreted defensin peptide. RESULTS: All epithelial tissue collected from cadaveric **corneas** expressed mRNA for hBD-1. hBD-2 was detectable in two of eight donors **corneas**, whereas hBD-3 was detected in five. All primary cultures of HCECs expressed hBD-1 and -3. A faint band for hBD-2 was detectable in three of eight cultures. Cultures of simian virus (SV)40-transformed HCECs always expressed hBD-1 and -3, but did not express hBD-2 under control conditions. IL-1beta and TNFalpha each stimulated the expression of hBD-2 in HCECs and were more effective in combination than alone. The effects of IL-1beta were concentration- (maximal at 10 ng/mL) and time-dependent (maximal at 12 hours and 24 hours for hBD-2 mRNA expression and protein secretion, respectively). The upregulation of hBD-2 mRNA persisted for at least 24 hours after removal of IL-1beta. The NFkappaB inhibitors pyrrolidinedithiocarbamate (PDT; 100 muM), caffeic acid phenethyl ester (CAPE; 90 muM), and MG-132 (25 muM), blocked IL-1beta-stimulated expression of hBD-2. The p38 mitogen-activated protein (MAP) kinase inhibitor SB203580 (5 muM) and the c-Jun NH2-terminal kinase (JNK) inhibitor SP600125 (25 muM) partially blocked (by 47% and 59%, respectively) the effect of IL-1beta. However, PD98059, an ERK inhibitor, had no effect. Genistein (50 muM) and dexamethasone (1 muM) also partially blocked (by 26% and 28%, respectively) the effect of IL-1beta. CONCLUSIONS: Human **corneal** epithelium expresses hBD-1 and -3. hBD-2 is not typically present, but its expression can be stimulated by proinflammatory cytokines such as IL-1beta, acting through mitogen-activated protein (MAP) kinase and nuclear factor (NF)-kappaB pathways. Because IL-1 is known to be increased at the **ocular** surface after injury, the current observations provide a mechanism to explain the previous finding that hBD-2 is upregulated in regenerating **corneal** epithelium. Cytokine stimulation of hBD-2 expression most likely provides additional protection against infection and raises the possibility that this defensin in particular may be involved in the wound-healing response, per se.

CC Cytology - Animal 02506

Cytology - Human 02508

Genetics - General 03502

Genetics - Human 03508

Biochemistry studies - General 10060

Biochemistry studies - Nucleic acids, purines and pyrimidines 10062

Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004
 Genetics of bacteria and viruses 31500
 Virology - General and methods 33502

IT Major Concepts
 Molecular Genetics (Biochemistry and Molecular Biophysics); Sense
 Organs (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
 cornea: sensory system; **corneal** epithelial cells:
 sensory system, regeneration

IT Chemicals & Biochemicals
 ERK [extracellular signal-regulated kinase]; PD98059: enzyme
 inhibitor-drug; RNA; SB203580: enzyme inhibitor-drug; SP600125: enzyme
 inhibitor-drug; beta-defensin-1 mRNA [beta-defensin-1 messenger RNA]:
 expression, regulation; beta-defensin-2 mRNA [beta-defensin-2 messenger
 RNA]: expression, regulation; beta-defensin-3 mRNA [beta-defensin-3
 messenger RNA]: expression, regulation; c-Jun amino-terminal kinase [EC
 2.7.1.112]: regulation; caffeic acid phenethyl ester; defensin:
 biomarker, expression; dexamethasone; genistein: enzyme inhibitor-drug;
 interleukin-1-beta [IL-1-beta]: proinflammatory cytokine; nuclear
 factor-kappa-B [NF-kappa-B]: regulation; p53 mitogen-activated protein
 kinase: regulation; pyrrolidinedithiocarbamate: NF-kappa-B inhibitor;
 tumor necrosis factor-alpha

IT Methods & Equipment
 RT-PCR [reverse transcriptase-polymerase chain reaction]: genetic
 techniques, laboratory techniques; immunoblot analysis: immunologic
 techniques, laboratory techniques


IT Miscellaneous Descriptors
 multiple signaling pathway; wound healing response


ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 HCEC cell line (cell line): human **corneal** epithelial cells
 human (common): cadaveric
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Polyomaviridae 03117
 Super Taxa
 dsDNA Viruses; Viruses; Microorganisms
 Organism Name
 Simian virus 40 (species)
 Taxa Notes
 Double-Stranded DNA Viruses, Microorganisms, Viruses

RN 142243-02-5 (ERK)
 142243-02-5 (extracellular signal-regulated kinase)
 167869-21-8 (PD98059)
 152121-47-6 (SB203580)
129-56-6 (SP600125)
 155215-87-5 (c-Jun amino-terminal kinase)
 80449-02-1 (c-Jun amino-terminal kinase)
 155215-87-5 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 104594-70-9 (caffeic acid phenethyl ester)
 103220-14-0 (defensin)
 50-02-2 (dexamethasone)

446-72-0 (genistein)
25769-03-3 (pyrrolidinedithiocarbamate)

L639 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:543571 BIOSIS
DOCUMENT NUMBER: PREV200300539080
TITLE: SRC KINASE ACTIVATION INDUCES FORMATION OF LENS OPACITIES 

AUTHOR(S): Zhou, J. [Reprint Author]; Menko, S. [Reprint Author]
CORPORATE SOURCE: Pathology, Anatomy and Cell Biology, Thomas Jefferson
University, Philadelphia, PA, USA
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
(2003) Vol. 2003, pp. Abstract No. 3136. cd-rom. 
Meeting Info.: Annual Meeting of the Association for
Research in Vision and Ophthalmology. Fort Lauderdale, FL,
USA. May 04-08, 2003. Association for Research in Vision
and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 19 Nov 2003
Last Updated on STN: 19 Nov 2003

ED Entered STN: 19 Nov 2003

Last Updated on STN: 19 Nov 2003

AB Purpose: Our previous studies have shown that suppression of Src Family Kinase (SFK) activity blocks the formation of lens opacities in an in vitro cataract model system. The goal of this study is to map the downstream signaling effectors of Src kinases in the formation of cataract. Methods: E10 chick lenses were cultured in Medium 199 containing 10% fetal bovine serum in the presence or absence of the SFK-specific inhibitor PP1. Lenses were extracted over a time course from 10 minutes to 24 hours and examined by immunoblot analysis for effects on activation of potential downstream signaling effectors of Src kinases. These included Focal Adhesion Kinase (FAK), a direct Src target, and the MAP kinases ERK, JNK and p38. To examine the role of activation of specific MAP kinases on lens opacification, lenses were grown for 10 days in the presence or absence of inhibitors of ERK (U0126), JNK (SP600125) and p38 (SB203580). Lenses were observed and photographed daily, and degree of opacification was quantified using image analysis software. Results: In lenses grown under culture conditions in which they form cataracts, phosphorylation of two distinct tyrosines of the FAK signaling protein, FAK Y861 and FAK Y925, were greatly increased. Both of these FAK sites are phosphorylated by Src kinases. In lens cultures in which cataract formation was suppressed by inhibition of SFK activity, phosphorylation of both FAK Y861 and FAK Y925 was inhibited. These results suggest a role for FAK signaling downstream of Src kinases in the formation of cataracts. Since both Src and FAK are known to mediate activation of MAP kinases, we investigated the activation state of MAP kinases in our lens cultures. We found transient activation of ERK, JNK and p38. This MAP kinase activation was blocked when the lenses were grown in the presence of the SFK inhibitor PP1. To analyze the potential role of ERK, JNK, and p38 in cataract formation lenses were cultured in the presence of specific MAP kinase inhibitors. While inhibitors to ERK and JNK did not interfere with the formation of cataract, growth of the lens in the presence of the p38 inhibitor blocked the formation of lens opacity with a similar efficacy to the Src kinase inhibitor PP1. Conclusions: Src kinase activation leads to the formation of cataract through a pathway involving the phosphorylation of FAK and the activation of the MAP kinase p38.

CC General biology - Symposia, transactions and proceedings 00520
 Enzymes - General and comparative studies: coenzymes 10802
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006

IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs
 (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
 lens: sensory system

IT Diseases
 cataract: **eye** disease, etiology
 Cataract (MeSH)

IT Diseases
 lens opacity: **eye** disease

IT Chemicals & Biochemicals
 ERK [extracellular signal-regulated kinase]: MAP kinase, regulation;
 JNK [c-jun N-terminal kinase]: MAP kinase, regulation; PP1: enzyme
 inhibitor-drug; SB203580: enzyme inhibitor-drug; SP600125: enzyme
 inhibitor-drug; Src family kinase: downstream signaling factor,
 regulation; U0126: enzyme inhibitor-drug; fetal bovine serum; focal
 adhesion kinase Y861: downstream signaling factor, phosphorylation,
 regulation, signaling; focal adhesion kinase Y925: downstream signaling
 factor, phosphorylation, regulation, signaling; p38: MAP kinase,
 regulation

IT Methods & Equipment
 image analysis software: computer software; immunoblot analysis:
 immunologic techniques, laboratory techniques

ORGN Classifier
 Galliformes 85536
 Super Taxa
 Aves; Vertebrata; Chordata; Animalia
 Organism Name
 chicken (common)
 Taxa Notes
 Animals, Birds, Chordates, Nonhuman Vertebrates, Vertebrates

RN 142243-02-5 (ERK)
 142243-02-5 (extracellular signal-regulated kinase)
 155215-87-5 (JNK)
 155215-87-5 (c-jun N-terminal kinase)
 152121-47-6 (SB203580)
 129-56-6 (SP600125)
 109511-58-2 (U0126)

L639 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
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ACCESSION NUMBER: 2003:391760 BIOSIS

DOCUMENT NUMBER: PREV200300391760

TITLE: Bovine retinal pericytes undergo apoptosis in response to
 increasing concentrations of insulin.

AUTHOR(S): Berken, Melanie S. [Reprint Author]; Baldassare, Joseph J.;
 Stephenson, Alan H.; Sprague, Randy S.; Lonigro, Andrew J.

CORPORATE SOURCE: Pharmacological and Physiological Sciences, Saint Louis
 University School of Medicine, 1402 S. Grand Blvd., St.
 Louis, MO, 63104, USA

berkenms@slu.edu; baldasjj@slu.edu; stephens@slu.edu;
 spraguer@slu.edu; lonigro@slu.edu
 SOURCE: FASEB Journal, (March 2003) Vol. 17, No. 4-5, pp. Abstract
 No. 346.32. <http://www.fasebj.org/>. e-file.
 Meeting Info.: FASEB Meeting on Experimental Biology:
 Translating the Genome. San Diego, CA, USA. April 11-15,

2003. FASEB.
 ISSN: 0892-6638 (ISSN print).
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Aug 2003
 Last Updated on STN: 27 Aug 2003
 ED Entered STN: 27 Aug 2003
 Last Updated on STN: 27 Aug 2003
 AB During the course of diabetic retinopathy, pericytes (PCs) disappear from the retinal microvasculature. Neither the stimulus nor the signaling mechanism for this PC loss is known. We hypothesized that the dropout of PCs in diabetic retinopathy is related to PC apoptosis. To test this hypothesis, bovine retinal PCs were isolated, purified, and characterized as previously described. Treatment of PCs with increasing insulin concentrations resulted in a dose-dependent increase in PC positive TUNEL staining (an index of apoptosis), whereas equimolar concentrations of aprotinin, a protein of comparable molecular weight to insulin did not. To characterize the pathway(s) of insulin-induced PC apoptosis, PCs were incubated with insulin (2.09 uM) for 15 min, resulting in Akt activation (immunoblot). The insulin receptor inhibitor, HNMPA-(AM)3 (100 uM), inhibited insulin-induced Akt activation. Treatment of PCs with insulin (2.09 uM) also resulted in JNK1 activation that peaked at 10 min of insulin treatment (immunoblot). This insulin-induced JNK1 activation was inhibited by the JNK blocker, SP600125 (20 uM) (immunoblot). SP600125 also inhibited insulin-induced PC apoptosis (TUNEL assay). From these experiments, we conclude that insulin-induced PC apoptosis may, at least in part, account for PC disappearance in diabetic retinopathy.
 CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Pathology - General 12502
 Pathology - Therapy 12512
 Metabolism - General metabolism and metabolic pathways 13002
 Metabolism - Metabolic disorders 13020
 Cardiovascular system - Physiology and biochemistry 14504
 Cardiovascular system - Blood vessel pathology 14508
 Endocrine - General 17002
 Endocrine - Pancreas 17008
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006
 Pharmacology - Drug metabolism and metabolic stimulators 22003
 IT Major Concepts
 Endocrine System (Chemical Coordination and Homeostasis); Metabolism;
 Sense Organs (Sensory Reception)
 IT Parts, Structures, & Systems of Organisms
 retinal microvasculature: circulatory system, sensory system; retinal
 pericytes: sensory system, apoptosis
 IT Diseases
 diabetes: endocrine disease/pancreas, metabolic disease, complications
 Diabetes Mellitus (MeSH)
 IT Diseases
 diabetic retinopathy: endocrine disease/pancreas, eye
 disease, metabolic disease, vascular disease, pathology
 Diabetic Retinopathy (MeSH)
 IT Chemicals & Biochemicals
 Akt: activation; HNMPA-(AM): metabolic-drug, insulin receptor
 inhibitor; JNK1: activation; SP600125: enzyme inhibitor-drug, JNK
 blocker; aprotinin; insulin: concentrations
 IT Methods & Equipment

TUNEL staining: genetic techniques, laboratory techniques; immunoblot:
immunologic techniques, laboratory techniques

IT Miscellaneous Descriptors
signaling mechanism

ORGN Classifier
Bovidae 85715
Super Taxa
Artiodactyla; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
bovine (common)
Taxa Notes
Animals, Artiodactyls, Chordates, Mammals, Nonhuman Vertebrates,
Nonhuman Mammals, Vertebrates

RN 129-56-6 (SP600125)
9087-70-1 (aprotinin)
9004-10-8 (insulin)

L639 ANSWER 11 OF 12 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-07416 DRUGU B P V S
TITLE: Induction of apoptosis in retinoid-refractory acute
myelogenous leukemia by a novel AHPN analog.
AUTHOR: Zhang Y; Dawson M I; Ning Y; Polin L; Parchment R E; Corbett
T; Mohamed A N; Feng K C; Farhana L; Fontana J A
CORPORATE SOURCE: Univ.Wayne-State; Mol.Med.Res.Inst.Mountain-View;
Univ.British-Columbia; Univ.Oregon-State; Univ.New-Mexico
LOCATION: USA; Can.
SOURCE: Blood (102, No. 10, 3743-52, 2003) 9 Fig. 3 Tab. 79 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: John D Dingell VA Medical Center, Oncology 11M-HO, 4646 John
R St, Detroit, MI 48201, U.S.A. (J.A.F., 22 authors).
(e-mail: joseph.fontana@med.va.gov).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB (E)-4-(3-(1-adamantyl)-4-hydroxyphenyl)-3-chlorocinnamic acid
(3-Cl-AHPC), but not trans-retinoic acid (tretinoin, tRA), inhibited
proliferation and induced cell death in human acute megakaryocytic M07e,
KG-1, HL-60R acute myelogenous leukemia (AML) cells in-vitro. 3-Cl-AHPC
blocked leukemic cell and CFU-granulocyte/macrophage (GM) formation.
PD-169316 and SP-600125, but not PD-98059 (all 3
Calbiochem), inhibited both p38 and c-Jun N-terminal kinase (JNK)
activation. I.v. 3-Cl-AHPC and i.v. 6-(3-(1-adamantyl)-4-hydroxyphenyl)-
2-naphthalenecarboxylic acid (AHPN/CD437) induced weight loss in mice
in-vivo. 3-Cl-AHPC prolonged survival duration in i.v. murine AML 1498
tumor-bearing mice. Data suggest that 3-Cl-AHPC is a potent inducer of
apoptosis in AML cells and may represent a novel therapy in the treatment
of this disease.

L639 ANSWER 12 OF 12 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-17485 DRUGU P B
TITLE: Salicylic acid reverses phorbol 12-myristate-13-acetate
(PMA)- and tumor necrosis factor alpha (TNF-alpha)-induced
insulin receptor substrate 1 (IRS1) serine 307
phosphorylation and insulin resistance in human embryonic
kidney 293 (HEK293) cells.
AUTHOR: Jiang G; Dallas Yang Q; Liu F; Moller D E; Zhang B B
CORPORATE SOURCE: Merck-USA
LOCATION: Rahway, N.J., USA
SOURCE: J.Biol.Chem. (278, No. 1, 180-86, 2003) 7 Fig. 52 Ref.

=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Sep 23, 2005 (20050923/UP).

=> d his 1207

(FILE 'HCAPLUS' ENTERED AT 08:58:38 ON 29 SEP 2005)

L207 1 SEA L122 OR L173 OR L190

FILE 'STNGUIDE' ENTERED AT 08:58:56 ON 29 SEP 2005

FILE 'HCAPLUS' ENTERED AT 08:59:05 ON 29 SEP 2005

FILE 'STNGUIDE' ENTERED AT 08:59:05 ON 29 SEP 2005

=> d que 1207

L1 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L2 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L3 QUE ABB=ON PLU=ON JNK OR JNK1 OR P46JNK OR ((MITOGEN O
R JUN) (5A) ?KINAS?)
L4 (67)SEA FILE=HCAPLUS ABB=ON PLU=ON GAMACHE, D?/AU
L5 (41)SEA FILE=WPIX ABB=ON PLU=ON GAMACHE, D?/AU
L6 (26)SEA FILE=MEDLINE ABB=ON PLU=ON GAMACHE, D?/AU
L7 (31)SEA FILE=EMBASE ABB=ON PLU=ON GAMACHE, D?/AU
L8 (55)SEA FILE=BIOSIS ABB=ON PLU=ON GAMACHE, D?/AU
L9 (19)SEA FILE=PASCAL ABB=ON PLU=ON GAMACHE, D?/AU
L10 (0)SEA FILE=JICST-EPLUS ABB=ON PLU=ON GAMACHE, D?/AU
L11 (9)SEA FILE=LIFESCI ABB=ON PLU=ON GAMACHE, D?/AU
L12 (6)SEA FILE=CANCERLIT ABB=ON PLU=ON GAMACHE, D?/AU
L13 (14)SEA FILE=DRUGU ABB=ON PLU=ON GAMACHE, D?/AU
L14 (0)SEA FILE=VETU ABB=ON PLU=ON GAMACHE, D?/AU
L15 (0)SEA FILE=VETB ABB=ON PLU=ON GAMACHE, D?/AU
L16 (48)SEA FILE=SCISEARCH ABB=ON PLU=ON GAMACHE, D?/AU
L17 (0)SEA FILE=CONF ABB=ON PLU=ON GAMACHE, D?/AU
L18 (5)SEA FILE=CONFSCI ABB=ON PLU=ON GAMACHE, D?/AU
L19 (2)SEA FILE=DISSABS ABB=ON PLU=ON GAMACHE, D?/AU
L20 (323)SEA GAMACHE, D?/AU
L21 SEL ABB=ON PLU=ON L1 1- CHEM : 11 TERMS
L22 (432)SEA FILE=HCAPLUS ABB=ON PLU=ON L21
L23 (22)SEA FILE=WPIX ABB=ON PLU=ON L21
L24 (218)SEA FILE=MEDLINE ABB=ON PLU=ON L21
L25 (547)SEA FILE=EMBASE ABB=ON PLU=ON L21
L26 (337)SEA FILE=BIOSIS ABB=ON PLU=ON L21
L27 (22)SEA FILE=PASCAL ABB=ON PLU=ON L21
L28 (1)SEA FILE=JICST-EPLUS ABB=ON PLU=ON L21
L29 (10)SEA FILE=LIFESCI ABB=ON PLU=ON L21
L30 (10)SEA FILE=CANCERLIT ABB=ON PLU=ON L21
L31 (201)SEA FILE=DRUGU ABB=ON PLU=ON L21

L32 (0)SEA FILE=VETU ABB=ON PLU=ON L21
 L33 (0)SEA FILE=VETB ABB=ON PLU=ON L21
 L34 (72)SEA FILE=SCISEARCH ABB=ON PLU=ON L21
 L35 (0)SEA FILE=CONF ABB=ON PLU=ON L21
 L36 (2)SEA FILE=CONFSCI ABB=ON PLU=ON L21
 L37 (0)SEA FILE=DISSABS ABB=ON PLU=ON L21
 L38 (1874)SEA L21
 L39 (46)SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (L22 OR L3 OR L2)
 L40 (30)SEA FILE=WPIX ABB=ON PLU=ON L5 AND (L23 OR L3 OR L2)
 L41 (17)SEA FILE=MEDLINE ABB=ON PLU=ON L6 AND (L24 OR L3 OR L2)
 L42 (16)SEA FILE=EMBASE ABB=ON PLU=ON L7 AND (L25 OR L3 OR L2)
 L43 (31)SEA FILE=BIOSIS ABB=ON PLU=ON L8 AND (L26 OR L3 OR L2)
 L44 (8)SEA FILE=PASCAL ABB=ON PLU=ON L9 AND (L27 OR L3 OR L2)
 L45 (0)SEA FILE=JICST-EPLUS ABB=ON PLU=ON L10 AND (L28 OR L3 OR L2)

 L46 (6)SEA FILE=LIFESCI ABB=ON PLU=ON L11 AND (L29 OR L3 OR L2)
 L47 (5)SEA FILE=CANCERLIT ABB=ON PLU=ON L12 AND (L30 OR L3 OR L2)
 L48 (11)SEA FILE=DRUGU ABB=ON PLU=ON L13 AND (L31 OR L3 OR L2)
 L49 (0)SEA FILE=VETU ABB=ON PLU=ON L14 AND (L32 OR L3 OR L2)
 L50 (0)SEA FILE=VETB ABB=ON PLU=ON L15 AND (L33 OR L3 OR L2)
 L51 (23)SEA FILE=SCISEARCH ABB=ON PLU=ON L16 AND (L34 OR L3 OR L2)
 L52 (0)SEA FILE=CONF ABB=ON PLU=ON L17 AND (L35 OR L3 OR L2)
 L53 (0)SEA FILE=CONFSCI ABB=ON PLU=ON L18 AND (L36 OR L3 OR L2)
 L54 (0)SEA FILE=DISSABS ABB=ON PLU=ON L19 AND (L37 OR L3 OR L2)
 L55 (193)SEA L20 AND (L38 OR L3 OR L2)
 L56 (72)DUP REM L55 (121 DUPLICATES REMOVED)
 L57 (45)SEA FILE=HCAPLUS L56
 L58 (45)SEA FILE=HCAPLUS L57 AND (L22 OR L39)
 L59 (2)SEA FILE=WPIX L56
 L60 (2)SEA FILE=WPIX L59 AND (L23 OR L40)
 L61 (2)SEA FILE=MEDLINE L56
 L62 (2)SEA FILE=MEDLINE L61 AND (L24 OR L41)
 L63 (0)SEA FILE=EMBASE L56
 L64 (0)SEA FILE=EMBASE L63 AND (L25 OR L42)
 L65 (18)SEA FILE=BIOSIS L56
 L66 (18)SEA FILE=BIOSIS L65 AND (L26 OR L43)
 L67 (0)SEA FILE=PASCAL L56
 L68 (0)SEA FILE=PASCAL L67 AND (L27 OR L44)
 L69 (0)SEA FILE=JICST-EPLUS L56
 L70 (0)SEA FILE=JICST-EPLUS L69 AND (L28 OR L45)
 L71 (0)SEA FILE=LIFESCI L56
 L72 (0)SEA FILE=LIFESCI L71 AND (L29 OR L46)
 L73 (0)SEA FILE=CANCERLIT L56
 L74 (0)SEA FILE=CANCERLIT L73 AND (L30 OR L47)
 L75 (2)SEA FILE=DRUGU L56
 L76 (2)SEA FILE=DRUGU L75 AND (L31 OR L48)
 L77 (0)SEA FILE=VETU L56
 L78 (0)SEA FILE=VETU L77 AND (L32 OR L49)
 L79 (0)SEA FILE=VETB L56
 L80 (0)SEA FILE=VETB L79 AND (L33 OR L50)
 L81 (3)SEA FILE=SCISEARCH L56
 L82 (3)SEA FILE=SCISEARCH L81 AND (L34 OR L51)
 L83 (0)SEA FILE=CONF L56
 L84 (0)SEA FILE=CONF L83 AND (L35 OR L52)
 L85 (0)SEA FILE=CONFSCI L56
 L86 (0)SEA FILE=CONFSCI L85 AND (L36 OR L53)
 L87 (0)SEA FILE=DISSABS L56
 L88 (0)SEA FILE=DISSABS L87 AND (L37 OR L54)
 L89 (72)SEA L56 AND (L38 OR L55)
 L90 (45)SEA FILE=HCAPLUS L56

L91 (1)SEA FILE=HCAPLUS L90 AND (L22 OR L3)
 L92 (2)SEA FILE=WPIX L56
 L93 (0)SEA FILE=WPIX L92 AND (L23 OR L3)
 L94 (2)SEA FILE=MEDLINE L56
 L95 (0)SEA FILE=MEDLINE L94 AND (L24 OR L3)
 L96 (0)SEA FILE=EMBASE L56
 L97 (0)SEA FILE=EMBASE L96 AND (L25 OR L3)
 L98 (18)SEA FILE=BIOSIS L56
 L99 (0)SEA FILE=BIOSIS L98 AND (L26 OR L3)
 L100 (0)SEA FILE=PASCAL L56
 L101 (0)SEA FILE=PASCAL L100 AND (L27 OR L3)
 L102 (0)SEA FILE=JICST-EPLUS L56
 L103 (0)SEA FILE=JICST-EPLUS L102 AND (L28 OR L3)
 L104 (0)SEA FILE=LIFESCI L56
 L105 (0)SEA FILE=LIFESCI L104 AND (L29 OR L3)
 L106 (0)SEA FILE=CANCERLIT L56
 L107 (0)SEA FILE=CANCERLIT L106 AND (L30 OR L3)
 L108 (2)SEA FILE=DRUGU L56
 L109 (0)SEA FILE=DRUGU L108 AND (L31 OR L3)
 L110 (0)SEA FILE=VETU L56
 L111 (0)SEA FILE=VETU L110 AND (L32 OR L3)
 L112 (0)SEA FILE=VETB L56
 L113 (0)SEA FILE=VETB L112 AND (L33 OR L3)
 L114 (3)SEA FILE=SCISEARCH L56
 L115 (0)SEA FILE=SCISEARCH L114 AND (L34 OR L3)
 L116 (0)SEA FILE=CONF L56
 L117 (0)SEA FILE=CONF L116 AND (L35 OR L3)
 L118 (0)SEA FILE=CONFSCI L56
 L119 (0)SEA FILE=CONFSCI L118 AND (L36 OR L3)
 L120 (0)SEA FILE=DISSABS L56
 L121 (0)SEA FILE=DISSABS L120 AND (L37 OR L3)
 L122 (1)SEA L56 AND (L38 OR L3)
 L123 (42)SEA FILE=HCAPLUS L58 AND ALCON/PA,CS,SO
 L124 (2)SEA FILE=WPIX L60 AND ALCON/PA,CS,SO
 L125 (2)SEA FILE=MEDLINE L62 AND ALCON/PA,CS,SO
 L126 (0)SEA FILE=EMBASE L64 AND ALCON/PA,CS,SO
 L127 (16)SEA FILE=BIOSIS L66 AND ALCON/PA,CS,SO
 L128 (0)SEA FILE=PASCAL L68 AND ALCON/PA,CS,SO
 L129 (0)SEA FILE=JICST-EPLUS L70 AND ALCON/PA,CS,SO
 L130 (0)SEA FILE=LIFESCI L72 AND ALCON/PA,CS,SO
 L131 (0)SEA FILE=CANCERLIT L74 AND ALCON/PA,CS,SO
 L132 (2)SEA FILE=DRUGU L76 AND ALCON/PA,CS,SO
 L133 (0)SEA FILE=VETU L78 AND ALCON/PA,CS,SO
 L134 (0)SEA FILE=VETB L80 AND ALCON/PA,CS,SO
 L135 (2)SEA FILE=SCISEARCH L82 AND ALCON/PA,CS,SO
 L136 (0)SEA FILE=CONF L84 AND ALCON/PA,CS,SO
 L137 (0)SEA FILE=CONFSCI L86 AND ALCON/PA,CS,SO
 L138 (0)SEA FILE=DISSABS L88 AND ALCON/PA,CS,SO
 L139 (66)SEA L89 AND ALCON/PA,CS,SO
 L140 (42)SEA FILE=HCAPLUS L123 AND L2
 L141 (2)SEA FILE=WPIX L124 AND L2
 L142 (2)SEA FILE=MEDLINE L125 AND L2
 L143 (0)SEA FILE=EMBASE L126 AND L2
 L144 (16)SEA FILE=BIOSIS L127 AND L2
 L145 (0)SEA FILE=PASCAL L128 AND L2
 L146 (0)SEA FILE=JICST-EPLUS L129 AND L2
 L147 (0)SEA FILE=LIFESCI L130 AND L2
 L148 (0)SEA FILE=CANCERLIT L131 AND L2
 L149 (2)SEA FILE=DRUGU L132 AND L2
 L150 (0)SEA FILE=VETU L133 AND L2

L151(0)SEA FILE=VETB L134 AND L2
 L152(2)SEA FILE=SCISEARCH L135 AND L2
 L153(0)SEA FILE=CONF L136 AND L2
 L154(0)SEA FILE=CONFSCI L137 AND L2
 L155(0)SEA FILE=DISSABS L138 AND L2
 L156(66)SEA L139 AND L2
 L157(1)SEA FILE=HCAPLUS L58 AND L22
 L158(0)SEA FILE=WPIX L60 AND L23
 L159(0)SEA FILE=MEDLINE L62 AND L24
 L160(0)SEA FILE=EMBASE L64 AND L25
 L161(0)SEA FILE=BIOSIS L66 AND L26
 L162(0)SEA FILE=PASCAL L68 AND L27
 L163(0)SEA FILE=JICST-EPLUS L70 AND L28
 L164(0)SEA FILE=LIFESCI L72 AND L29
 L165(0)SEA FILE=CANCERLIT L74 AND L30
 L166(0)SEA FILE=DRUGU L76 AND L31
 L167(0)SEA FILE=VETU L78 AND L32
 L168(0)SEA FILE=VETB L80 AND L33
 L169(0)SEA FILE=SCISEARCH L82 AND L34
 L170(0)SEA FILE=CONF L84 AND L35
 L171(0)SEA FILE=CONFSCI L86 AND L36
 L172(0)SEA FILE=DISSABS L88 AND L37
 L173(1)SEA L89 AND L38
 L174(1)SEA FILE=HCAPLUS L140 AND L22
 L175(0)SEA FILE=WPIX L141 AND L23
 L176(0)SEA FILE=MEDLINE L142 AND L24
 L177(0)SEA FILE=EMBASE L143 AND L25
 L178(0)SEA FILE=BIOSIS L144 AND L26
 L179(0)SEA FILE=PASCAL L145 AND L27
 L180(0)SEA FILE=JICST-EPLUS L146 AND L28
 L181(0)SEA FILE=LIFESCI L147 AND L29
 L182(0)SEA FILE=CANCERLIT L148 AND L30
 L183(0)SEA FILE=DRUGU L149 AND L31
 L184(0)SEA FILE=VETU L150 AND L32
 L185(0)SEA FILE=VETB L151 AND L33
 L186(0)SEA FILE=SCISEARCH L152 AND L34
 L187(0)SEA FILE=CONF L153 AND L35
 L188(0)SEA FILE=CONFSCI L154 AND L36
 L189(0)SEA FILE=DISSABS L155 AND L37
 L190(1)SEA L156 AND L38
 L191 1 SEA FILE=HCAPLUS L91 OR L157 OR L174
 L192(0)SEA FILE=WPIX L93 OR L158 OR L175
 L193(0)SEA FILE=MEDLINE L95 OR L159 OR L176
 L194(0)SEA FILE=EMBASE L97 OR L160 OR L177
 L195(0)SEA FILE=BIOSIS L99 OR L161 OR L178
 L196(0)SEA FILE=PASCAL L101 OR L162 OR L179
 L197(0)SEA FILE=JICST-EPLUS L103 OR L163 OR L180
 L198(0)SEA FILE=LIFESCI L105 OR L164 OR L181
 L199(0)SEA FILE=CANCERLIT L107 OR L165 OR L182
 L200(0)SEA FILE=DRUGU L109 OR L166 OR L183
 L201(0)SEA FILE=VETU L111 OR L167 OR L184
 L202(0)SEA FILE=VETB L113 OR L168 OR L185
 L203(0)SEA FILE=SCISEARCH L115 OR L169 OR L186
 L204(0)SEA FILE=CONF L117 OR L170 OR L187
 L205(0)SEA FILE=CONFSCI L119 OR L171 OR L188
 L206(0)SEA FILE=DISSABS L121 OR L172 OR L189
 L207 1 SEA L122 OR L173 OR L190

=>

=> d ibib ed ab l207

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L207 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:252187 HCAPLUS

DOCUMENT NUMBER: 140:281408

TITLE: Methods of treating dry eye disorders by
using cytokine synthesis inhibitors

INVENTOR(S): Gamache, Daniel A.

PATENT ASSIGNEE(S): Alcon, Inc., USA

SOURCE: U.S. Pat. Appl. Publ., 6 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058875	A1	20040325	US 2003-650006	20030826
CA 2497977	AA	20040401	CA 2003-2497977	20030826
WO 2004026406	A1	20040401	WO 2003-US26689	20030826
W: AU, BR, CA, CN, JP, KR, MX, PL, US, ZA				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
EP 1542768	A1	20050622	EP 2003-770254	20030826
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK				
BR 2003014603	A	20050726	BR 2003-14603	20030826
PRIORITY APPLN. INFO.:			US 2002-412463P	P 20020920
			WO 2003-US26689	W 20030826

ED Entered STN: 26 Mar 2004

AB The present invention is directed to methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. According to the methods of the present invention, certain cytokine synthesis inhibitors are administered to a patient suffering from dry eye or other disorders requiring wetting of the eye. The cytokine synthesis inhibitors are preferably administered topically to the eye.

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JNK-1's

1/6

09/29/2005

generals
(not specific)

=> fil hcap
FILE 'HCAPLUS' ENTERED AT 12:35:52 ON 28 SEP 2005
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FILE COVERS 1907 - 28 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 12:35:54 ON 28 SEP 2005
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STRUCTURE FILE UPDATES: 27 SEP 2005 HIGHEST RN 864057-55-6
DICTIONARY FILE UPDATES: 27 SEP 2005 HIGHEST RN 864057-55-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 12:35:56 ON 28 SEP 2005
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AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Sep 23, 2005 (20050923/UP).

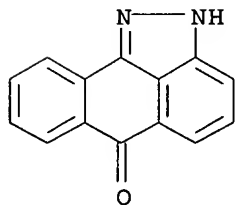
=> d que 15

L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US2003-650006/APPS
L3 TRANSFER PLU=ON L1 1- RN : 13 TERMS
L4 13 SEA FILE=REGISTRY ABB=ON PLU=ON L3
L5 1 SEA FILE=REGISTRY ABB=ON PLU=ON L4 AND C14H8N2O/MF

=> d ide 15

YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 129-56-6 REGISTRY
ED Entered STN: 16 Nov 1984
CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,9-Pyrazoloanthrone
CN 2H-Dibenzo[cd,g]indazol-6-one
CN C.I. 70300
CN NSC 75890
CN Pyrazoloanthrone
CN Pyrazoleanthrone
CN SP 600125
FS 3D CONCORD
MF C14 H8 N2 O
CI COM
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS,
CHEMLIST, CSChem, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS,
IMSRESEARCH, PROUSDDR, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

181 REFERENCES IN FILE CA (1907 TO DATE)
24 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
185 REFERENCES IN FILE CAPLUS (1907 TO DATE)

7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=> d que 17

L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN

=> d ide 17

YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y)/N:y

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN

RN 289898-51-7 REGISTRY

ED Entered STN: 21 Sep 2000

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

OTHER NAMES:

CN c-Jun N-terminal kinase

CN Gene c-jun protein kinase N-terminal kinase 1

CN Gene c-jun protein N-terminal kinase 1

CN JNK-46 protein kinase

CN JNK1

CN JNK1 kinase

CN JNK1 protein kinase

CN Jun N-terminal kinase 1

CN Mitogen-activated protein kinase 8

CN P46 c-Jun N-terminal kinase

CN p46JNK kinase

CN Protein kinase JNK1

MF Unspecified

CI MAN

SR CA

LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

920 REFERENCES IN FILE CA (1907 TO DATE)

29 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

931 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> => fil reg

FILE 'REGISTRY' ENTERED AT 07:46:37 ON 29 SEP 2005

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STRUCTURE FILE UPDATES: 28 SEP 2005 HIGHEST RN 864132-17-2

DICTIONARY FILE UPDATES: 28 SEP 2005 HIGHEST RN 864132-17-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> fil zcap

FILE 'ZCAPLUS' ENTERED AT 07:46:40 ON 29 SEP 2005

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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14

FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)

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substance identification.

```
=> fil hcap
FILE 'HCAPLUS' ENTERED AT 07:46:43 ON 29 SEP 2005
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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)
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New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> fil uspatfull
FILE 'USPATFULL' ENTERED AT 07:46:48 ON 29 SEP 2005
CA INDEXING COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US6951031
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210555
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005
```

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>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<
```

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>>> USPATFULL and USPAT2 can be accessed and searched together <<<
>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
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```

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=> fil uspatall

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FILE 'USPAT2' ENTERED AT 07:46:52 ON 29 SEP 2005
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=> fil uspat2

FILE 'USPAT2' ENTERED AT 07:47:03 ON 29 SEP 2005
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FILE COVERS 2001 TO PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US2005202247
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210551
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

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=> fil wpix

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FILE LAST UPDATED: 28 SEP 2005 <20050928/UP>
MOST RECENT DERWENT UPDATE: 200562 <200562/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
<http://thomsonderwent.com/coverage/latestupdates/> <<<

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FIRST VIEW - FILE WPIFV.

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=> fil medlin

FILE 'MEDLINE' ENTERED AT 07:47:17 ON 29 SEP 2005

FILE LAST UPDATED: 28 SEP 2005 (20050928/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP
RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>

http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2005 vocabulary.

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=> fil embase

FILE 'EMBASE' ENTERED AT 07:47:21 ON 29 SEP 2005

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FILE COVERS 1974 TO 22 Sep 2005 (20050922/ED)

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=> fil biosis

FILE 'BIOSIS' ENTERED AT 07:47:24 ON 29 SEP 2005

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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 28 September 2005 (20050928/ED)

FILE RELOADED: 19 October 2003.

=> fil toxcenter

FILE 'TOXCENTER' ENTERED AT 07:47:43 ON 29 SEP 2005

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TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the
MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a
description of changes.

=> fil pascal

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FILE LAST UPDATED: 26 SEP 2005 <20050926/UP>

FILE COVERS 1977 TO DATE.

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=> fil jicst

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FILE COVERS 1985 TO 26 SEP 2005 (20050926/ED)

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=> fil lifesci

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FILE COVERS 1978 TO 19 Sep 2005 (20050919/ED)

=> fil cancerlit

FILE 'CANCERLIT' ENTERED AT 07:48:00 ON 29 SEP 2005

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the
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FILE LAST UPDATED: 27 SEP 2005 <20050927/UP>

>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

=> fil vetu
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FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>
FILE COVERS 1983-2001

=> fil vetb
FILE 'VETB' ENTERED AT 07:48:12 ON 29 SEP 2005
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FILE LAST UPDATED: 25 SEP 94 <940925/UP>
FILE COVERS 1968-1982

=> fil scisearch
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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)

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FILE CONTAINS CURRENT INFORMATION.

Audet 10/650,006

09/29/2005

LAST RELOADED: Sep 23, 2005 (20050923/UP).

=> d que 155

L34 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L35 (1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L36 SEL PLU=ON L34 1- CHEM : 11 TERMS
 L37 (432)SEA FILE=HCAPLUS ABB=ON PLU=ON L36
 L38 (186)SEA FILE=HCAPLUS ABB=ON PLU=ON L34
 L39 SEL PLU=ON L35 1- CHEM : 13 TERMS
 L40 (4144)SEA FILE=HCAPLUS ABB=ON PLU=ON L39
 L41 (931)SEA FILE=HCAPLUS ABB=ON PLU=ON L35
 L42 (35883)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L43 (21166)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
 ,NT/CT
 L44 (17731)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
 PFT,NT/CT
 L45 (610)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
 CT
 L46 (3)SEA FILE=HCAPLUS ABB=ON PLU=ON (L37 OR L38) AND (L42 OR L43
 OR L44 OR L45)
 L47 (27)SEA FILE=HCAPLUS ABB=ON PLU=ON (L40 OR L41) AND (L42 OR L43
 OR L44 OR L45)
 L48 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L49 (1)SEA FILE=HCAPLUS ABB=ON PLU=ON (L37 OR L38) (L) L48
 L50 (24)SEA FILE=HCAPLUS ABB=ON PLU=ON (L40 OR L41) (L) L48
 L51 (47)SEA FILE=HCAPLUS ABB=ON PLU=ON L46 OR L47 OR L49 OR L50
 L52 (65)SEA FILE=HCAPLUS ABB=ON PLU=ON (L37 OR L38 OR L40 OR L41)
 AND L48
 L53 (68)SEA FILE=HCAPLUS ABB=ON PLU=ON (L51 OR L52)
 L54 (5)SEA FILE=HCAPLUS ABB=ON PLU=ON L53 AND (L37 OR L38)
 L55 - - - 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L54 AND (AY<2003 OR PY<2003
 OR PRY<2003)

=> d his 1132

(FILE 'USPATFULL, USPAT2' ENTERED AT 07:40:05 ON 29 SEP 2005)

L132 8 SEA L131 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d que 1170

L156 (8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR
 RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
 L157 (8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
 L158 (8)SEA FILE=WPIX ABB=ON PLU=ON L156 OR L157
 L159 (3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L160 (16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03
 OR B12-J08 OR C12-J08 OR E12-J08)/MC
 L161 (1)SEA FILE=WPIX ABB=ON PLU=ON L158 AND (L159 OR L160)
 L162 (3)SEA FILE=WPIX ABB=ON PLU=ON L158 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L163 (8)SEA FILE=WPIX ABB=ON PLU=ON L158 OR L161 OR L162
 L164 (819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
 L165 (115)SEA FILE=WPIX ABB=ON PLU=ON L164 AND (L159 OR L160)
 L166 (105)SEA FILE=WPIX ABB=ON PLU=ON L165 AND (EYE/BIX OR EYES/BIX OR

OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L167(28)SEA FILE=WPIX ABB=ON PLU=ON L166 AND ((DRY?(3A)EYE?) OR
 ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR
 ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN?
 OR ?XEROPH?)/BIX
 L168(35)SEA FILE=WPIX ABB=ON PLU=ON L163 OR L167
 L169(28)SEA FILE=WPIX ABB=ON PLU=ON L168 AND (AY<2003 OR PY<2003 OR
 PRY<2003)
 L170 5 SEA FILE=WPIX ABB=ON PLU=ON L169 AND L163

=> d his l375

(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
 VETU, VETB, SCISEARCH' ENTERED AT 07:43:51 ON 29 SEP 2005)

L375 1 SEA L354 AND L297

=> d que l375

L293 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L294 SEL PLU=ON L293 1- CHEM : 11 TERMS
 L295(813)SEA L294
 L296(6)SEA L295 AND L293
 L297(6)DUP REM L296 (0 DUPLICATES REMOVED)
 L298 SEL PLU=ON L293 1- CHEM : 13 TERMS
 L299(13886)SEA L298
 L300(139)SEA L299 AND L293
 L301(88)DUP REM L300 (51 DUPLICATES REMOVED)
 L302(55)SEA FILE=BIOSIS L301
 L303(25)SEA FILE=BIOSIS L302 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L304(6)SEA FILE=TOXCENTER L301
 L305(2)SEA FILE=TOXCENTER L304 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L306(8)SEA FILE=PASCAL L301
 L307(2)SEA FILE=PASCAL L306 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L308(0)SEA FILE=JICST-EPLUS L301
 L309(0)SEA FILE=JICST-EPLUS L308 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L310(0)SEA FILE=LIFESCI L301
 L311(0)SEA FILE=LIFESCI L310 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L312(1)SEA FILE=CANCERLIT L301
 L313(1)SEA FILE=CANCERLIT L312 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L314(11)SEA FILE=DRUGU L301
 L315(11)SEA FILE=DRUGU L314 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR

LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L316(0)SEA FILE=VETU L301
 L317(0)SEA FILE=VETU L316 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L318(0)SEA FILE=VETB L301
 L319(0)SEA FILE=VETB L318 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L320(7)SEA FILE=SCISEARCH L301
 L321(3)SEA FILE=SCISEARCH L320 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L322(44)SEA L301 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
 LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
 ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L323(3)SEA FILE=BIOSIS L297
 L324(28)SEA FILE=BIOSIS L323 OR L303
 L325(0)SEA FILE=TOXCENTER L297
 L326(2)SEA FILE=TOXCENTER L325 OR L305
 L327(0)SEA FILE=PASCAL L297
 L328(2)SEA FILE=PASCAL L327 OR L307
 L329(0)SEA FILE=JICST-EPLUS L297
 L330(0)SEA FILE=JICST-EPLUS L329 OR L309
 L331(0)SEA FILE=LIFESCI L297
 L332(0)SEA FILE=LIFESCI L331 OR L311
 L333(0)SEA FILE=CANCERLIT L297
 L334(1)SEA FILE=CANCERLIT L333 OR L313
 L335(3)SEA FILE=DRUGU L297
 L336(12)SEA FILE=DRUGU L335 OR L315
 L337(0)SEA FILE=VETU L297
 L338(0)SEA FILE=VETU L337 OR L317
 L339(0)SEA FILE=VETB L297
 L340(0)SEA FILE=VETB L339 OR L319
 L341(0)SEA FILE=SCISEARCH L297
 L342(3)SEA FILE=SCISEARCH L341 OR L321
 L343(48)SEA L297 OR L322
 L344(9)SEA FILE=BIOSIS L324 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L345(0)SEA FILE=TOXCENTER L326 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L346(0)SEA FILE=PASCAL L328 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L347(0)SEA FILE=JICST-EPLUS L330 AND (AY<2003 OR PY<2003 OR PRY<2003
 OR MY<2003)
 L348(0)SEA FILE=LIFESCI L332 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L349(1)SEA FILE=CANCERLIT L334 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L350(7)SEA FILE=DRUGU L336 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L351(0)SEA FILE=VETU L338 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L352(0)SEA FILE=VETB L340 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L353(1)SEA FILE=SCISEARCH L342 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L354(18)SEA L343 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
 L355(3)SEA FILE=BIOSIS L297

L356(0)SEA FILE=BIOSIS L344 AND L355
L357(0)SEA FILE=TOXCENTER L297
L358(0)SEA FILE=TOXCENTER L345 AND L357
L359(0)SEA FILE=PASCAL L297
L360(0)SEA FILE=PASCAL L346 AND L359
L361(0)SEA FILE=JICST-EPLUS L297
L362(0)SEA FILE=JICST-EPLUS L347 AND L361
L363(0)SEA FILE=LIFESCI L297
L364(0)SEA FILE=LIFESCI L348 AND L363
L365(0)SEA FILE=CANCERLIT L297
L366(0)SEA FILE=CANCERLIT L349 AND L365
L367(3)SEA FILE=DRUGU L297
L368 1 SEA FILE=DRUGU L350 AND L367
L369(0)SEA FILE=VETU L297
L370(0)SEA FILE=VETU L351 AND L369
L371(0)SEA FILE=VETB L297
L372(0)SEA FILE=VETB L352 AND L371
L373(0)SEA FILE=SCISEARCH L297
L374(0)SEA FILE=SCISEARCH L353 AND L373
L375 1 SEA L354 AND L297

=> dup rem l55 l132 l170 l375

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PROCESSING COMPLETED FOR L55
PROCESSING COMPLETED FOR L132
PROCESSING COMPLETED FOR L170
PROCESSING COMPLETED FOR L375
L637 13 DUP REM L55 L132 L170 L375 (4 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE HCAPLUS
ANSWERS '4-9' FROM FILE USPATFULL
ANSWERS '10-12' FROM FILE WPIX
ANSWER '13' FROM FILE DRUGU

=> file stnguide

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Sep 23, 2005 (20050923/UP).

=> d ibib ed ab hitind hitstr retable

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?

(Y)/N:y

L637 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2004:392328 HCAPLUS

DOCUMENT NUMBER: 140:386068

TITLE: Methods using a JNK inhibitor for the treatment,
prevention and management of macular degeneration

INVENTOR(S): Zeldis, Jerome B.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 31 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004092568	A1	20040513	US 2003-699105	20031030 <--
CA 2504028	AA	20040521	CA 2003-2504028	20031031 <--
WO 2004041191	A2	20040521	WO 2003-US34662	20031031 <--
WO 2004041191	A3	20041202		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
EP 1565188	A2	20050824	EP 2003-778016	20031031 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK			
PRIORITY APPLN. INFO.:			US 2002-422896P	P 20021031 <--
			US 2003-699105	A 20031030
			WO 2003-US34662	W 20031031

OTHER SOURCE(S): MARPAT 140:386068

ED Entered STN: 14 May 2004

AB The invention relates to methods for treating, preventing and/or managing macular degeneration. Specific embodiments encompass the administration of a JNK Inhibitor, alone or in combination with a second active agent and/or surgery or phys. therapy. Pharmaceutical compns., single unit dosage forms, and kits suitable for use in methods of the invention are also disclosed.

IC ICM A61K031-416

INCL 514406000

CC 1-12 (Pharmacology)

Section cross-reference(s): 63

IT **Eye, disease**

(age-related maculopathy; JNK inhibitor for treatment, prevention and management of macular degeneration)

IT **Eye, disease**

(macula, degeneration; JNK inhibitor for treatment, prevention and management of macular degeneration)

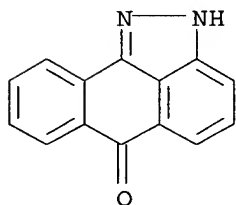
IT **Eye**
 (pigment epithelium, atrophy and detachment; JNK inhibitor for treatment, prevention and management of macular degeneration)

IT **Eye, disease**
 (retina, neovascularization; JNK inhibitor for treatment, prevention and management of macular degeneration)

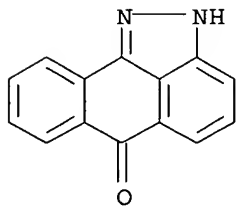
IT **129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one 129-56-6D**
, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs. 271-44-3D, Indazole, derivs. 6313-41-3, 6H-Anthra[9,1-cd]isothiazol-6-one 6313-41-3D, 6H-Anthra[9,1-cd]isothiazol-6-one, derivs. 63973-07-9, 6H-Anthra[9,1-cd]isoxazol-6-one 63973-07-9D, 6H-Anthra[9,1-cd]isoxazol-6-one, derivs. 183723-45-7D, derivs. 312927-17-6 312927-17-6D, derivs. 395100-04-6 628684-74-2 628684-74-2D, derivs. 628684-75-3, Dibenz[cd,g]indol-6(2H)-one 628684-75-3D, Dibenz[cd,g]indol-6(2H)-one, derivs.
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (JNK inhibitor for treatment, prevention and management of macular degeneration)

IT **129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one 129-56-6D**
, Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (JNK inhibitor for treatment, prevention and management of macular degeneration)

RN 129-56-6 HCAPLUS
 CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 129-56-6 HCAPLUS
 CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



=> d ibib ed ab hitind hitstr retable 2-3
 YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?
 (Y)/N:y

L637/ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2
 ACCESSION NUMBER: 2004:252187 HCAPLUS
 DOCUMENT NUMBER: 140:281408
 TITLE: Methods of treating dry eye disorders by
 using cytokine synthesis inhibitors
 INVENTOR(S): Gamache, Daniel A.
 PATENT ASSIGNEE(S): Alcon, Inc., USA
 SOURCE: U.S. Pat. Appl. Publ., 6 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004058875	A1	20040325	US 2003-650006	20030826 <--
CA 2497977	AA	20040401	CA 2003-2497977	20030826 <--
WO 2004026406	A1	20040401	WO 2003-US26689	20030826 <--
W: AU, BR, CA, CN, JP, KR, MX, PL, US, ZA				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR				
EP 1542768	A1	20050622	EP 2003-770254	20030826 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK				
BR 2003014603	A	20050726	BR 2003-14603	20030826 <--
PRIORITY APPLN. INFO.:			US 2002-412463P	P 20020920 <--
			WO 2003-US26689	W 20030826

ED Entered STN: 26 Mar 2004

AB The present invention is directed to methods for the treatment of dry eye and other disorders requiring the wetting of the eye, including symptoms of dry eye associated with refractive surgery such as LASIK surgery. According to the methods of the present invention, certain cytokine synthesis inhibitors are administered to a patient suffering from dry eye or other disorders requiring wetting of the eye. The cytokine synthesis inhibitors are preferably administered topically to the eye.

IC ICM A61K038-08

ICS A61K031-506; A61K031-416

INCL 514015000; 514256000; 514405000

CC 1-12 (Pharmacology)

Section cross-reference(s): 15

ST dry eye disorder cytokine synthesis inhibitor topical delivery

IT Interleukin 6

Interleukin 8

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(anthra[1,9-cd]pyrazol

-6(2H)-one inhibiting; methods of

treating dry eye disorders by using cytokine synthesis inhibitors)

IT Drug delivery systems

(carriers; methods of treating dry eye disorders by using cytokine synthesis inhibitors)

IT Eye, disease

(dry; methods of treating dry eye

disorders by using cytokine synthesis inhibitors)

IT Transcription factors

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibitor; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT Retinoid X receptors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (ligand; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT Human
 Mammalia
 (methods of treating dry eye disorders by using cytokine
 synthesis inhibitors)

IT Cytokines
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (synthesis inhibitor; methods of treating dry eye disorders
 by using cytokine synthesis inhibitors)

IT Interleukin 1
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (synthesis inhibitor; methods of treating dry eye disorders
 by using cytokine synthesis inhibitors)

IT Tumor necrosis factors
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (synthesis inhibitor; methods of treating dry eye disorders
 by using cytokine synthesis inhibitors)

IT Drug delivery systems
 (topical; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT Signal transduction, biological
 (transducer; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT 142243-02-5, Mitogen-activated protein kinase 159606-08-3 161384-16-3,
 JaK kinase 165245-96-5, p38 Kinase 289898-51-7, c-
Jun N-terminal kinase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibitor; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT 129-56-6, {Anthra[1,9-cd]
 pyrazol-6(2H)-one} 322-79-2,
 Triflusal 153559-49-0, Bexarotene 154563-54-9 165806-53-1,
 (5-(2-Amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole)
 192755-52-5, Pralnacasan 675104-42-4
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (methods of treating dry eye disorders by using cytokine
 synthesis inhibitors)

IT 71-50-1, Acetate, biological studies
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (salt; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

IT 289898-51-7, c-Jun N-
terminal kinase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (inhibitor; methods of treating dry eye disorders by using
 cytokine synthesis inhibitors)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

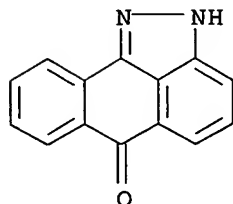
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT 129-56-6, {Anthra[1,9-cd]
 pyrazol-6(2H)-one}
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(methods of treating dry eye disorders by using cytokine synthesis inhibitors)

RN 129-56-6 HCAPLUS

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637/ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2003:737576 HCAPLUS

DOCUMENT NUMBER: 139:240349

TITLE: Combination therapy including a JNK kinase inhibitor for treating, preventing or managing proliferative disorders and cancers

INVENTOR(S): Stein, Bernd M.; Westwick, John K.; Ennis, Bruce W.

PATENT ASSIGNEE(S): Signal Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 109 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075917	A1	20030918	WO 2003-US6894	20030307 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2478338	AA	20030918	CA 2003-2478338	20030307 <--
US 2004067953	A1	20040408	US 2003-384440	20030307 <--
EP 1487436	A1	20041222	EP 2003-713937	20030307 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			US 2002-362705P	P 20020308 <--
			US 2003-384440	A 20030307
			WO 2003-US6894	W 20030307

OTHER SOURCE(S): MARPAT 139:240349

ED Entered STN: 19 Sep 2003

AB The invention provides methods and compns. designed for the treatment, management or prevention of cancer. The methods of the invention comprise the administration of an effective amount of one or more inhibitors of JNK in combination with the administration of an effective amount of one or more other agents useful for cancer therapy. The invention also provides pharmaceutical compns. comprising one or more inhibitors of JNK in

combination with one or more other agents useful for cancer therapy. In particular, the invention provides methods of treatment and prevention of cancer by the administration of an effective amount of one or more inhibitors of JNK in combination with standard and exptl. chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biol. therapies/immunotherapies and/or radiation therapies for treatment or prevention of cancer. Also included are methods of treatment of cancer by the administration of one or more inhibitors of JNK in combination with surgery, alone or in further combination with standard and exptl. chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biol. therapies/immunotherapies and/or radiation therapies. JNK inhibitors include e.g. indazole derivs.

IC ICM A61K031-40
ICS A61K031-42; A61K031-415; A61K031-425; A61K031-505; A61K031-519

CC 1-6 (Pharmacology)
Section cross-reference(s): 63

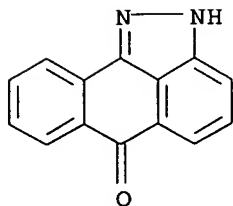
IT Angiogenesis inhibitors
Antitumor agents
Bone, neoplasm
Brain, neoplasm
Cytotoxic agents
Drug toxicity
Esophagus, neoplasm
 Eye, neoplasm
Head, neoplasm
Human
Kidney, neoplasm
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Mouth, neoplasm
Neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Pharynx, neoplasm
Prostate gland, neoplasm
Radiotherapy
Reproductive tract, neoplasm
Skin, neoplasm
Stomach, neoplasm
Testis, neoplasm
Thyroid gland, neoplasm
 (JNK kinase inhibitor in combination therapy for cancer treatment)

IT 50-18-0, Cyclophosphamide 50-35-1, Thalidomide 51-21-8, 5-Fluorouracil 59-05-2, Methotrexate 129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one 15663-27-1, Cisplatin 19171-19-8 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 41575-94-4, Carboplatin 97682-44-5, Irinotecan 191732-72-6, CC 5013 205923-56-4, Cetuximab 395100-04-6
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (JNK kinase inhibitor in combination therapy for cancer treatment)

IT 129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (JNK kinase inhibitor in combination therapy for cancer treatment)

RN 129-56-6 HCAPLUS

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Signal Pharmaceuticals	2002			WO 02046170 A2	

=> d ibib ab hitstr 4-9

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?
(Y)/N:y

L637, ANSWER 4 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2005:22824 USPATFULL

TITLE: Drug-coated stents and methods of use therefor

INVENTOR(S): Zeldis, Jerome B., Princeton, NJ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005019366	A1	20050127
APPLICATION INFO.:	US 2003-749344	A1	20031230 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-437332P	20021231 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017	
NUMBER OF CLAIMS:	27	
EXEMPLARY CLAIM:	1	
LINE COUNT:	1874	

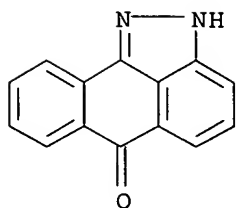
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to stents comprising an effective amount of a c-Jun N-terminal kinase ("JNK") Inhibitor, the stents being useful for treating or preventing a cardiovascular or renal disease. The invention also relates to the treatment or prevention of cardiovascular or renal disease, such as atherosclerosis or restenosis, comprising implanting into a patient in need thereof of a stent comprising an effective amount of a JNK Inhibitor.

IT 129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one
(stents comprising JNK kinase inhibitor for treating or preventing cardiovascular or renal disease)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637 ANSWER 5 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2004:228048 USPATFULL

TITLE: Methods for treating inflammatory conditions or inhibiting JNK

INVENTOR(S): Bennett, Brydon L., San Diego, CA, UNITED STATES
 Bhagwat, Shripad S., San Diego, CA, UNITED STATES
 Manning, Anthony M., San Diego, CA, UNITED STATES
 Murray, Brion W., San Diego, CA, UNITED STATES
 O'Leary, Eoin C., San Diego, CA, UNITED STATES
 Satoh, Yoshitaka, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004176434	A1	20040909
APPLICATION INFO.:	US 2003-738640	A1	20031216 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2003-395810, filed on 24 Mar 2003, PENDING Continuation-in-part of Ser. No. US 2000-642557, filed on 18 Aug 2000, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-240928P	19990819 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Page(s)	
LINE COUNT:	1652	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

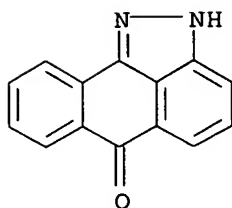
AB This invention generally relates to methods for treating or preventing an inflammatory disease or disorder comprising administering to a patient in need thereof an effective amount of a Pyrazoloanthrone Derivative having the following structure: ##STR1##

or a pharmaceutically acceptable salt thereof, wherein R.sub.1 and R.sub.2 are as defined herein.

IT 129-56-6P, Anthra[1,9-cd]pyrazol-6(2H)-one
 (preparation of pyrazoloanthrones as JNK inhibitors)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637 ANSWER 6 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2004:95433 USPATFULL

TITLE: Methods for treating inflammatory conditions or inhibiting JNK

INVENTOR(S): Bennett, Brydon L., San Diego, CA, UNITED STATES
 Bhagwat, Shripad S., San Diego, CA, UNITED STATES
 Manning, Anthony M., San Diego, CA, UNITED STATES
 Murray, Brion W., San Diego, CA, UNITED STATES
 O'Leary, Eoin C., San Diego, CA, UNITED STATES
 Satoh, Yoshitaka, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004072888	A1	20040415
APPLICATION INFO.:	US 2003-395810	A1	20030324 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2000-642557, filed on 18 Aug 2000, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-240928P	19990819 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JONES DAY, 222 EAST 41ST STREET, NEW YORK, NY, 10017	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Page(s)	
LINE COUNT:	1652	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

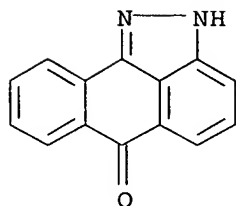
AB This invention generally relates to methods for treating or preventing an inflammatory disease or disorder comprising administering to a patient in need thereof an effective amount of a Pyrazoloanthrone Derivative having the following structure: ##STR1##

or a pharmaceutically acceptable salt thereof, wherein R.sub.1 and R.sub.2 are as defined herein.

IT 129-56-6P, Anthra[1,9-cd]pyrazol-6(2H)-one
 (preparation of pyrazoloanthrone derivs. for treating inflammatory conditions or inhibiting Jun N-terminal kinases)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637 ANSWER 7 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2004:88976 USPATFULL

TITLE: Combination therapy for treating, preventing or managing proliferative disorders and cancers

INVENTOR(S): Stein, Bernd M., San Diego, CA, UNITED STATES
Westwick, John K., San Ramon, CA, UNITED STATES
Ennis, Bruce W., Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004067953	A1	20040408
APPLICATION INFO.:	US 2003-384440	A1	20030307 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-362705P	20020308 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JONES DAY, 222 EAST 41ST STREET, NEW YORK, NY, 10017	
NUMBER OF CLAIMS:	33	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Page(s)	
LINE COUNT:	4208	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

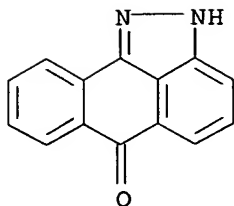
AB The present invention relates to methods and compositions designed for the treatment, management or prevention of cancer. The methods of the invention comprise the administration of an effective amount of one or more inhibitors of JNK in combination with the administration of an effective amount of one or more other agents useful for cancer therapy. The invention also provides pharmaceutical compositions comprising one or more inhibitors of JNK in combination with one or more other agents useful for cancer therapy. In particular, the invention is directed to methods of treatment and prevention of cancer by the administration of an effective amount of one or more inhibitors of JNK in combination with standard and experimental chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biological therapies/immunotherapies and/or radiation therapies for treatment or prevention of cancer. Also included are methods of treatment of cancer by the administration of one or more inhibitors of JNK in combination with surgery, alone or in further combination with standard and experimental chemotherapies, hormonal therapies, bone marrow transplants, stem cell replacement therapies, biological therapies/immunotherapies and/or radiation therapies.

IT 129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one

(JNK kinase inhibitor in combination therapy for cancer treatment)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637 ANSWER 8 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2004:57386 USPATFULL

TITLE: Three hybrid assay system

INVENTOR(S): Come, Jon H., Cambridge, MA, UNITED STATES
 Becker, Frank, Planegg, GERMANY, FEDERAL REPUBLIC OF
 Kley, Nikolai A., Wellesley, MA, UNITED STATES
 Reichel, Christoph, Planegg, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004043388	A1	20040304
APPLICATION INFO.:	US 2002-234985	A1	20020903 (10) <--
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2002-91177, filed on 4 Mar 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-272932P	20010302 (60) <--
	US 2001-278233P	20010323 (60) <--
	US 2001-329437P	20011015 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ROPES & GRAY, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624	
NUMBER OF CLAIMS:	96	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	18 Drawing Page(s)	
LINE COUNT:	8493	

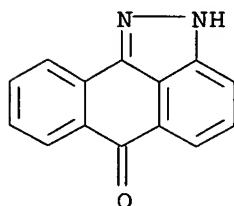
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides compositions and methods for isolating ligand binding polypeptides for a user-specified ligand, and for isolating small molecule ligands for a user-specified target polypeptide using an improved class of hybrid ligand compounds.

IT 129-56-6D, Anthra[1,9-cd]pyrazol-6(2H)-one, conjugates
 (three hybrid assay system for isolating ligand-binding polypeptides and for isolating small mol. ligands)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



L637 ANSWER 9 OF 13 USPATFULL on STN

ACCESSION NUMBER: 2004:38124 USPATFULL

TITLE: Methods of using JNK or MKK inhibitors to modulate cell differentiation and to treat myeloproliferative disorders and myelodysplastic syndromes

INVENTOR(S): Hariri, Robert J., Florham Park, NJ, UNITED STATES
Stirling, David I., Warren, NJ, UNITED STATES
Zeldis, Jerome B., Princeton, NJ, UNITED STATESPATENT ASSIGNEE(S): Anthrogenesis Corporation (U.S. corporation)
Celgene Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004028660	A1	20040212
APPLICATION INFO.:	US 2003-449248	A1	20030530 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-384250P	20020530 (60) <--
	US 2002-434833P	20021219 (60) <--

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711

NUMBER OF CLAIMS: 58

EXEMPLARY CLAIM: 1

LINE COUNT: 4032

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides methods of modulating mammalian, particularly human, stem cell and progenitor cell differentiation to regulate and control the differentiation and maturation of these cells along specific cell and tissue lineages. The methods of the invention relate to the use of certain small organic molecules to modulate the differentiation of stem cell populations along specific cell and tissue lineages, particularly embryonic-like stem cells originating from a postpartum placenta or stem cells isolated from sources such as cord blood. The invention also relates to the treatment or prevention of myelodysplastic syndrome or myeloproliferative syndrome, or symptoms thereof, comprising administration of JNK or MKK inhibitors, alone or in combination, as well as with or without the use of unconditioned cells or cells conditioned in accordance with other aspects of the invention. Finally, the invention relates to the use of such differentiated stem cells in transplantation and other medical treatments.

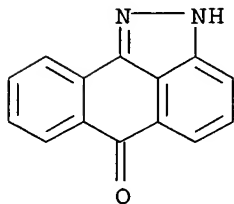
IT 129-56-6, Anthra[1,9-cd]pyrazol-6(2H)-one 129-56-6D,

Anthra[1,9-cd]pyrazol-6(2H)-one, derivs.

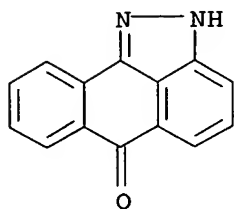
(JNK or MKK inhibitors to modulate cell differentiation and to treat myeloproliferative disorders and myelodysplastic syndromes)

RN 129-56-6 USPATFULL

CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



RN 129-56-6 USPATFULL
 CN Anthra[1,9-cd]pyrazol-6(2H)-one (6CI, 7CI, 8CI, 9CI) (CA INDEX NAME)



=> d iall abeq tech abex 10-12

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?
 (Y)/N:y

L637 ANSWER 10 OF 13 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-561535 [54] WPIX
 DOC. NO. CPI: C2005-167552
 TITLE: Stent, useful to prevent or treat e.g. cardiovascular and renal diseases, comprises c-Jun N-terminal kinase inhibitor.
 DERWENT CLASS: A96 B02 B03 B07 D22
 INVENTOR(S): ZELDIS, J B
 PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP; (ZELD-I) ZELDIS J B
 COUNTRY COUNT: 107
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004060318	A2	20040722	(200454)*	EN	65	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
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PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ							
VC VN YU ZA ZM ZW							
AU 2003300466	A1	20040729	(200477)			A61K000-00	
US 2005019366	A1	20050127	(200509)			A61K031-415	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004060318	A2	WO 2003-US41763	20031231
AU 2003300466	A1	AU 2003-300466	20031231
US 2005019366	A1 Provisional	US 2002-437332P	20021231 <--
		US 2003-749344	20031230

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2003300466 A1 Based on WO 2004060318

PRIORITY APPLN. INFO: US 2003-749344 20031230;
 US 2002-437332P
 20021231

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-415
 SECONDARY: A61F002-00

BASIC ABSTRACT:

WO2004060318 A UPAB: 20050907

NOVELTY - Stent (I) comprising c-Jun N-terminal kinase inhibitor (A), is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprises (I) and directions for its use.

ACTIVITY - Cardiovascular-Gen.; Nephrotropic; Antiarteriosclerotic.

MECHANISM OF ACTION - c-Jun N-terminal kinase (JNK) inhibitor. (I) were assessed for JNK inhibitor activity in jurkat T cells. The median inhibitory concentration of (I) was 0.1-30 micro M.

USE - (I) are useful to prevent or treat cardiovascular or renal disease, atherosclerosis (claimed).

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: A12-V01; A12-V02; B04-C03B; B06-D05; B06-D18;
 B06-E05; B06-F05; B07-D03; B07-D05; B07-D11;
 B07-D12; B11-C04; B14-D06; B14-F01; B14-F02;
 B14-F07; B14-N10; D09-C01

TECH

UPTX: 20040823

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: (I) having coating comprises incorporated (A). (I) is indazole derivative of formula (a), pyrimidine-2-amine derivative of formula (b) or anthraquinone derivative of formula (c) and their salts, solvates or stereoisomers. (I) is a stent graft and it comprises polymer. The polymer is polyamide, a polyester, a polystyrene, a polypropylene, a polyacrylate, a polyvinyl, a polycarbonate, a polytetrafluorethylene, a polymethylmethacrylate, a polyethylene, a poly(ethylene terephthalate), a polyalkylene oxalate, a polyurethane, a polysiloxane, a poly(dimethyl siloxane), a polycyanoacrylate, a polyphosphazene, a poly(amino acid), a ethylene glycol dimethacrylate, a poly(methyl methacrylate), a poly(2-hydroxyethyl methacrylate), a poly (HEMA) or a polyhydroxyalkanoate. The coating is controlled-release coating. The method of (I) preparation further comprises surgical intervention. The intervention involves percutaneous coronary intervention, revascularisation, percutaneous transluminal coronary angioplasty, carotid percutaneous transluminal angioplasty coronary by-pass grafting, coronary angioplasty with stent implantation, renal angioplasty, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries; or surgical intervention using impregnated artificial grafts. The implanting occurs prior, during or after to the administration of angioplasty.

A = bond, -(CH₂)a-, -(CH₂)bCH=CH(CH₂)c- or -(CH₂)bC =C(CH₂);

R1 = (hetero)aryl or heterocycle fused to phenyl (all optionally substituted with 1-4 substituents of R3);

R2 = R3, -R4, (CH₂)bC(O)R5, (CH₂)bC(O)OR5, (CH₂)bC(O)NR5R6,
 -(CH₂)bC(O)NR5(CH₂)CC(O)R6, (CH₂)bNR5C(O)R6, -(CH₂)bNR5C(O)NR6R7,
 -(CH₂)bNR5R6, -(CH₂)bOR5, -(CH₂)bSO2R5 or (CH₂)bSO2NR5R6;

a = 1-6;

b, c = 0-4;

d = 0-2;

R3 = halo, OH, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl,

arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR8, -OC(O)R8, C(O)NR8R9, C(O)NR8OR9, SO2NR8R9, NR8SO2R9, CN, NO2, NR8R9, NR8C(O)R9, NR8C(O)(CH2)OR9, NR8C(O)(CH2)z,R9, -O(CH2)bR8R9 or heterocycle fused to phenyl;

R4 = alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (all optionally substituted with 1-4 substituents of R3 or R4 halo or OH); R5, R6, R7 = H, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (optionally 1-4 substituents of R3); either R8, R9 = H, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl; or R8R9 = form a heterocycle (optionally substituted with 1-4 substituents of R3); and

R0 = O, S, S(O), S(O)2, NH or -CH2.

Compound (c) being:

(a) unsubstituted;

(b) monosubstituted and having a first substituent; or

(c) disubstituted and having a first substituent and a second substituent; when first or second substituent present then it is at the 3-5, 7-10 position; first and second substituent, when present, are alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy or amine derivative of formula (1-6).

structures (1-6), page 62)

ABEX UPTX: 20040823

SPECIFIC COMPOUNDS - The use of 34 compounds (A) is disclosed e.g. N-(6-oxo-6H-anthra(9,1-cd)isothiazol-5-yl)-benzamide, 7-dimethylamino-anthra(9,1-cd)isothiazol-6-one, 7-benzyloxy-2H-dibenzo(cd,g)indazol-6-one, (4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone, 1-(4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone, 4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-N,N'-dimethyl-benzamide, 5-(5-(1,1-dimethyl-propyl)-1H-(1,2,4)triazol-3-yl)-3-(4-fluoro-phenyl)-1H-indazole and N-tert-butyl-3-(5-(1H-(1,2,4)triazol-3-yl)-1H-indazol-3-yl)-benzamide.

L637 ANSWER 11 OF 13 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-374756 [35] WPIX

DOC. NO. CPI: C2004-140905

TITLE: Method for treating, preventing, managing and/or modifying pain involves use of c-Jun-N-terminal kinase inhibitor.

DERWENT CLASS: B05

INVENTOR(S): FALECK, H; MANNING, D C; ZELDIS, J B

PATENT ASSIGNEE(S): (FALE-I) FALECK H; (MANN-I) MANNING D C; (ZELD-I) ZELDIS J B; (CELG-N) CELGENE CORP

COUNTRY COUNT: 107

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2004087642	A1	20040506	(200435)*		35	A61K031-416	
WO 2004039325	A2	20040513	(200439)	EN		A61K000-00	
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LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP							
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG							
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ							
VC VN YU ZA ZM ZW							
AU 2003284980	A1	20040525	(200468)			A61K031-416	

EP 1553951 A2 20050720 (200547) EN A61K031-517
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
 MC MK NL PT RO SE SI SK TR
 BR 2003015573 A 20050830 (200558) A61K031-517

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004087642	A1 Provisional	US 2002-421104P	20021024 <--
		US 2003-693793	20031023
WO 2004039325	A2	WO 2003-US34006	20031024
AU 2003284980	A1	AU 2003-284980	20031024
EP 1553951	A2	EP 2003-779300	20031024
		WO 2003-US34006	20031024
BR 2003015573	A	BR 2003-15573	20031024
		WO 2003-US34006	20031024

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003284980	A1 Based on	WO 2004039325
EP 1553951	A2 Based on	WO 2004039325
BR 2003015573	A Based on	WO 2004039325

PRIORITY APPLN. INFO: **US 2002-421104P**
20021024; US 2003-693793
 20031023

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-416; A61K031-517
 SECONDARY: A61K031-415; A61K031-42; A61K031-425

BASIC ABSTRACT:

US2004087642 A UPAB: 20040603

NOVELTY - A method for treating, preventing, managing and/or modifying pain involves administration of c-Jun-N-terminal kinase (JNK) inhibitor, its salt, solvate or stereoisomer.

ACTIVITY - Analgesic; Virucide; Muscular-Gen.; Immunomodulator; Anticonvulsant; Neuroprotective; Antiinflammatory; Dermatological; Endocrine-Gen.; Osteopathic; Antidiabetic; Vulnerary; Antiarthritic; Antirheumatic; Cerebroprotective; Vasotropic.

MECHANISM OF ACTION - c-Jun-N-terminal Kinase (JNK) Inhibitor.
 5-Amino-anthra(9,1-cd)isothiazol-6-one (A) was assayed for its inhibitory activity against p38-2 protein kinase according to the method described in Protein Phosphorylation, Sefton and Hunter, Eds., Academic Press, pp. 97-367, 1998. The IC50 value of (A) was found to be greater than 30000 nM.

USE - For treating, preventing, managing and/or modifying pain i.e. complex regional pain syndrome (preferably type I (having III stages) or type II) e.g. pain, autonomic dysfunction, trigeminal neuralgia, post-herpetic neuralgia, cancer-related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, radiculopathy, inability to initiate movement, weakness, tremor, muscle spasm, dytonia, dystrophy, atrophy, edema, stiffness, joint tenderness, increased sweating, sensitivity to temperature, light touch (allodynia), color change to the skin hyperthermic or hypothermic, increased nail and hair growth, early bony changes, hyperhidrotic with livedo reticularis or cyanosis, lost hair, ridged, cracked or brittle nails, dry hand, diffuse osteoporosis, irreversible tissue damage, thin and shiny skin, joint contractures, marked bone demineralization, diabetic neuropathy, luetic neuropathy,

painful neuropathy induced iatrogenically by a drug or another painful neuropathic condition; nociceptive pain associated with a cut or contusion of the skin; a chemical or thermal burn; osteoarthritis; rheumatoid arthritis; or tendonitis; neuropathic pain associated with stroke, diabetic neuropathy, luetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, fibromyalgia, or painful neuropathy induced iatrogenically by a drug (all claimed).

ADVANTAGE - The method is safe and very effective.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D05; B06-E05; B06-F05; B07-D12; B14-A02;
B14-C01; B14-C03; B14-C06; B14-C09; B14-D01;
B14-D06; B14-F02D; B14-G03; B14-J01B; B14-J07;
B14-N01; B14-N16; B14-N17; B14-S04

TECH UPTX: 20040603

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compounds: The JNK inhibitor is a compound of formula (I) - (III).

A = direct bond, -(CH₂)_a-, -(CH₂)_bCH=CH(CH₂)_c- or -(CH₂)_bC_{triple}bondC(CH₂)_c-;

R₁ = (hetero)aryl or heterocycle fused to phenyl (all optionally mono- - tetra-substituted by R₃) (preferably phenylene (substituted by (R₃)₀₋₄));

R₂ = -R₃, R₄, -(CH₂)_bC(O)R₅-, -(CH₂)_bC(O)OR₅-, -(CH₂)_bC(O)NR₅R₆-, -(CH₂)_bC(O)NR₅(CH₂)_c-C(O)R₆-, -(CH₂)_bNR₅C(O)R₆-, -(CH₂)_bNR₅C(O)NR₆R₇-, -(CH₂)_bNR₅R₆-, -(CH₂)_bOR₅, (CH₂)_bSO₂R₅ or -(CH₂)_bSO₂NR₅R₆- (preferably -N(R₅)-C(O)-R₆);

a = 1 - 6;

b and c = 0 - 4;

d = 0 - 2;

R₃ = halo, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, optionally substituted aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR₈, -OC(O)R₈, -C(O)NR₈R₉, -C(O)NR₈OR₉, -SO₂NR₈R₉, -NR₈SO₂R₉, -CN, -NO₂, -NR₈R₉, -NR₈C(O)R₉, -NR₈C(O)(CH₂)_bOR₉, -NR₈C(O)(CH₂)_bR₉, -O(CH₂)_bNR₈R₉ or heterocycle fused to phenyl;

R₄ = alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl (all optionally mono- - tetra-substituted by R₃), halo or hydroxy;

R₅ - R₉ = alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl (all optionally mono- - tetra-substituted by R₃) or H;

R₈+R₉ = a heterocycle (all optionally mono- - tetra-substituted by R₃);

R'₁ = (hetero)aryl (optionally mono- - tetra-substituted by R₃) (preferably phenyl (substituted at 4 position by R₇));

R'₂ = H;

R'₃ = H or lower alkyl (preferably H);

R'₄ = halo, hydroxy, lower alkyl, lower alkoxy or absent (preferably absent);

R'₅ and R'₆ = -R₈, -(CH₂)_rC(O)R'₉, -(CH₂)_rC(O)OR'₉, -(CH₂)_rC(O)NR'₉R₁₀, -(CH₂)_rC(O)NR'₉(CH₂)_tC(O)R₁₀, -(CH₂)_rNR'₉C(O)R₁₀, -(CH₂)_rNR₁₁C(O)NR'₉R₁₀, -(CH₂)_rNR'₉R₁₀, -(CH₂)_rOR'₉, -(CH₂)_rSO₂R'₉ or -(CH₂)_rSO₂NR'₉R₁₀;

NR'₅+R'₆ = optionally substituted heterocycle;

R'₇ = halo, hydroxy, cyano, nitro, carboxy, alkoxy, (halo)alkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR'₈, -OC(O)R'₈, -C(O)NR'₈R'₉, -C(O)NR'₈OR'₉, -SOMR'₈, -SOMNR'₈R'₉, -NR'₈SO₂R'₉, -NR'₈R'₉, -NR'₈C(O)R'₉, -NR'₉C(O)(CH₂)_tOR'₉, -NR'₈C(O)(CH₂)_tR'₉, -O(CH₂)_tNR_{SR}'₉ or heterocycle fused to phenyl;

R'₈, R'₉, R₁₀ and R₁₁ = H, optionally substituted alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl;

R'₈+R'₉ = heterocycle;

r and t = 0 - 4;

$m = 0 - 2$;
 $R' = -O-, -S-, -S(O)-, -S(O)_2-, NH$ or $-CH_2-$;
 $R_3+R_4 =$ alkylidene or a heteroatom-containing cyclic alkylidene;
 R_3 and $R_4 = H, (cyclo)alkyl, aryl, arylalkyl, cycloalkylalkyl,$
 $aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl$ or
 $di-alkylaminoalkyl$;
 $R_5 = H, (cyclo)alkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy,$
 $alkoxyalkyl, alkoxyalkyl, alkoxyalkyl, amino, mono-alkylamino, di-alkylamino,$
 $arylamine, arylalkylamine, cycloalkylamine, cycloalkylalkylamine,$
 $aminoalkyl, mono-alkylaminoalkyl$ or $di-alkylaminoalkyl$.
 The compound of formula (III) is optionally mono or di-substituted at 3,
 4, 5, 7, 8, 9, or 10 position by alkyl, hydroxy, halo, nitro,
 trifluoromethyl, sulfonyl, carboxyl, alkoxy, aryl,
 aryloxy, arylalkoxy, arylalkyl, cycloalkylalkoxy, cycloalkoxy,
 alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy,
 $di-alkylaminoalkoxy, -N(R_3)-R_4, -NH-(alkyl)N(R_3)-R_4, -NH-C(O)-R_5,$
 $-NH-S(O)_2-R_5, -C(O)-N(R_4)-R_3$ or $-S(O)_2-N(R_4)-R_3$.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method
 additionally involves administration of a second active agent.
 Preferred Components: The second active agent is an antidepressant,
 antihypertensive, anxiolytic, calcium channel blocker, muscle relaxant,
 non-narcotic analgesic, anti-inflammatory agent, cyclooxygenase-2 (COX-2)
 inhibitor, alpha-adrenergic receptor agonist or antagonist, ketamine,
 anesthetic, immunomodulatory agent, immunosuppressive agent,
 corticosteroid, hyperbaric oxygen, anticonvulsant, IMiD (RTM) and/or
 SelCID (RTM) (preferably gabapentin, thalidomide, salicylic acid acetate,
 ketamine, celastrol, carbamazepine, oxcarbazepine, phenytoin, sodium
 valproate, prednisone, nifedipine, clonidine, oxycodone, meperidine,
 morphine sulfate, hydromorphone, fentanyl, acetaminophen, ibuprofen,
 naproxen sodium, griseofulvin, amitriptyline, imipramine, doxepin, their
 salt, solvate or stereoisomer).

ABEX

UPTX: 20040603

SPECIFIC COMPOUNDS - 3-(4-Fluoro-phenyl)-5-(1H-(1,2,4)triazol-3-yl)-1H-
 indazole; and 5-amino-anthra(9,1-cd)isothiazol-6-one are specifically
 claimed as JNK inhibitor.

ADMINISTRATION - The dosage of JNK inhibitor is 0.001 - 1000 (preferably
 0.001 - 500, especially 0.001 - 100 and particularly 0.001 - 1) mg/day and
 administered parenterally (e.g. intradermally, intramuscularly,
 intraperitoneally, intravenously or subcutaneously), epidurally or
 mucosally (e.g. intranasally, rectally, vaginally, sublingually, buccally
 or orally).

EXAMPLE - No relevant example given.

L637 ANSWER 12 OF 13 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-040801 [03] WPIX
 DOC. NO. CPI: C2003-009781
 TITLE: Use of inhibitors of Jun Kinase (JNK) to treat metabolic
 disorders associated with insulin resistance, improve
 insulin sensitivity, diagnose insulin resistance, prevent
 obesity or inhibit fat accumulation in liver tissue.
 DERWENT CLASS: B02 B04
 INVENTOR(S): CHANG, L; HOTAMISLIGIL, G S; KARIN, M
 PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE; (REGC) UNIV CALIFORNIA
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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WO 2002085396  A1 20021031 (200303)* EN 38 A61K035-78<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW
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DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
ZW
EP 1390052      A1 20040225 (200415) EN      A61K035-78
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
AU 2002307475  A1 20021105 (200433)          A61K035-78<--

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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002085396	A1	WO 2002-US12687	20020424 <--
EP 1390052	A1	EP 2002-764295	20020424 <--
		WO 2002-US12687	20020424 <--
AU 2002307475	A1	AU 2002-307475	20020424 <--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1390052	A1 Based on	WO 2002085396
AU 2002307475	A1 Based on	WO 2002085396

PRIORITY APPLN. INFO: **US 2001-285966P**
20010424

INT. PATENT CLASSIF.:

MAIN: A61K035-78

BASIC ABSTRACT:

WO 200285396 A UPAB: 20030113

NOVELTY - Metabolic disorders associated with insulin resistance can be treated by the administration of an inhibitor of a NH2-terminal Jun Kinase (JNK).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Method of improving insulin sensitivity by the administration of an inhibitor of JNK;

(2) Treating or preventing obesity by the administration of an inhibitor of JNK;

(3) Diagnosing insulin resistance or the risk of developing insulin resistance by measuring the level of JNK activity or expression in a tissue, where an increase in activity or expression compared to normal indicates that the patient is suffering from or at risk of developing resistance; and

(4) Method of inhibiting fat accumulation in liver tissue by contacting the tissue with an inhibitor of JNK.

ACTIVITY - Antidiabetic; Anorectic; Hepatotropic; Dermatological; Virucide; Antiinfertility; Antiarteriosclerotic.

No biological data available.

MECHANISM OF ACTION - Inhibitor of JNK.

No biological data available.

USE - JNK is used for treating metabolic disorders associated with insulin resistance, improving insulin sensitivity, diagnosing insulin resistance, preventing or treating obesity or inhibiting fat accumulation in liver tissue (all claimed).

Also treating conditions associated with insulin resistance, e.g. cancer cachexia, HIV-1 infection, polycystic ovarian syndrome, atherosclerosis or severe burns.

DESCRIPTION OF DRAWING(S) - The figure shows bodyweight in JNK1-deficient mice compared to wild type control mice after both types of mouse were put on a high fat diet for 12 weeks.

Dwg.1/12

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B02-H; B06-A01; B06-D06; B06-D09; B06-D18; B11-C08;
B12-K04A; B14-A02B1; B14-D06; B14-E12; B14-F07;
B14-J01A2; B14-N12; B14-N14; B14-N17A; B14-P02;
B14-S04

TECH UPTX: 20030113

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: Inhibitor binds to an ATP binding site in JNK or to a catalytic domain of JNK. In inhibiting fat accumulation in liver tissue, the inhibitor preferentially reduces enzymatic activity of JNK1 compared to JNK2.

Preferred Inhibitor: The JNK is JNK1 or JNK2. The inhibitor is SP600125.

ABEX UPTX: 20030113

SPECIFIC COMPOUNDS - The JNK inhibitor is SP600125.

ADMINISTRATION - JNK is administered parenterally, enterally or topically in a dosage of 50-150 mug/kg.

EXAMPLE - Mice deficient in JNK1 or JNK2 were bred and placed on a high fat diet for 12 weeks. The group deficient in JNK1 had body weights of about 34 g compared with about 45 g for a control group. When fed on a standard diet, the body weights were about 28 and 26 g respectively.

=> d ibib ed ab hitind 12

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?
(Y)/N:n

=> d ibib ed ab hitind 13

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' - CONTINUE?
(Y)/N:y

'ED' IS NOT A VALID FORMAT

'HITIND' IS NOT A VALID FORMAT

In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):ibib ab hitind

'HITIND' IS NOT A VALID FORMAT

In a multifile environment, a format can only be used if it is valid in at least one of the files. Refer to file specific help messages or the STNGUIDE file for information on formats available in individual files.

REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):ibib ab ind

L637 ANSWER 13 OF 13 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-07682 DRUGU P T B

TITLE: Matrix metalloproteinases as therapeutic targets in arthritic diseases. Bulls' eye or missing the mark

AUTHOR: Mengshol J A; Mix K S; Brinckerhoff C E

LOCATION: Hanover, N.H., USA
SOURCE: Arthritis Rheum. (46, No. 1, 13-20, (2002) 2 Fig. 61 Ref.
CODEN: ARHEAW ISSN: 0004-3591
AVAIL. OF DOC.: Dartmouth School, Departments of Biochemistry and Medicine,
HB 7200, Hanover, NH 03755, U.S.A. (C.E.B.). (e-mail:
c.e.brinckerhoff@dartmouth.edu).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The role of matrix metalloproteinases (MMP) as therapeutic targets in
arthritic diseases is reviewed. The therapeutic inhibition of MMP
activity and gene expression is discussed. The effects of Ro-323555,
matrilysin, G-1168, marimastat, doxycycline, SB-203580, **SP-**
600125, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO),
infliximab and etanercept are described. Future osteoarthritis (OA) and
rheumatoid arthritis (RA) therapies may include cocktails of specific MMP
inhibitors that target gene expression and/or enzyme activity.
AN 2002-07682 DRUGU P T B
P Pharmacology
T Therapeutics
B Biochemistry
14 Enzyme Inhibitors
20 Immunological
24 Bones and Joints
27 Molecular Biology
50 Biological Response Modifiers
69 Reviews
CT ARTHRITIS *TR; ARTHRITIS *OC; JOINT-DISEASE *TR; JOINT-DISEASE *OC;
MOUSE *FT; CASES *FT; IN-VIVO *FT; REVIEW *FT; DNA *FT;
NUCLEIC-ACID-METAB. *FT; MATRIX-METALLOPROTEINASE-INHIBITOR *FT;
DISEASE-MODIFYING *FT; EC-3.4.24.7 *FT; EC-3.4.24.24 *FT; EC-3.4.24.34
*FT; EC-3.4.24.35 *FT; EC-0.0.0.0 *FT; MATRIX-METALLOPROTEINASE-13
*FT; LAB.ANIMAL *FT; VERTEBRATE-COLLAGENASE *FT; GELATINASE-A *FT;
NEUTROPHIL-COLLAGENASE *FT; GELATINASE-B *FT
[01] MAIN-TOPIC *FT; MATRIX-METALLOPROTEINASE-INHIBITORS *FT; TR *FT; PH
*FT
[02] RO-323555 *TR; MATRILYSIN *TR; G-1168 *TR; MARIMASTAT *TR; DOXYCYCLINE
*TR; SB-203580 *TR; **SP-600125** *TR; INFLIXIMAB *TR;
ETANERCEPT *TR; RO-323555 *PH; MATRILYSIN *PH; G-1168 *PH; MARIMASTAT
*PH; DOXYCYCLINE *PH; SB-203580 *PH; **SP-600125**
*PH; INFLIXIMAB *PH; ETANERCEPT *PH; TR *FT; PH *FT

=> d que 1101

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L79 (      3)SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L80 (      1)SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L81      SEL  PLU=ON  L79 1- CHEM :      11 TERMS
L82 (    432)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L81
L83 (    186)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L79
L84      SEL  PLU=ON  L80 1- CHEM :      13 TERMS
L85 (   4144)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L84
L86 (    931)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L80
L87 (  35883)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE"+PFT,NT/CT
L88 (  21166)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE OR DISORDER"+PFT
      ,NT/CT
L89 (  17731)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYES, DISEASES OR DISORDERS"+
      PFT,NT/CT
L90 (    610)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE (L) DRY"+PFT,NT/
      CT
L91 (      3)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L82 OR L83) AND (L87 OR L88
      OR L89 OR L90)
L92 (     27)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L85 OR L86) AND (L87 OR L88
      OR L89 OR L90)
L93      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
      R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
      CHRIMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L94 (      1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L82 OR L83) (L) L93
L95 (     24)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L85 OR L86) (L) L93
L96 (     47)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L91 OR L92 OR L94 OR L95
L97 (     65)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L82 OR L83 OR L85 OR L86)
      AND L93
L98 (     68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L96 OR L97)
L99 (      5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L98 AND (L82 OR L83)
L100 (    63)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L98 NOT L99
L101     31 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L100 AND (AY<2003 OR PY<2003
      OR PRY<2003)

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=> d his 1143

(FILE 'USPATFULL, USPAT2' ENTERED AT 07:40:05 ON 29 SEP 2005)

L143 24 SEA L142 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d que 1143

```

L133      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
      R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
      CHRIMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L134 (    21)SEA L133
L135 (      8)SEA L134 AND L133/TI,IT,BI,ST,CC
L136 (      9)SEA A61P027-02/IPC
L137 (      0)SEA L134 AND L136
L138 (      8)SEA L135 OR L137
L139 (      8)SEA L138 AND (AY<2003 OR PY<2003 OR PRY<2003)
L140 (     64)SEA L133
L141 (    30)SEA L140 AND L133/TI,IT,BI,ST,CC
L142 (    29)SEA L141 NOT L139
L143     24 SEA L142 AND (AY<2003 OR PY<2003 OR PRY<2003)

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=> d que 1201

L187(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR
 RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
 L188(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
 L189(8)SEA FILE=WPIX ABB=ON PLU=ON L187 OR L188
 L190(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L191(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03
 OR B12-J08 OR C12-J08 OR E12-J08)/MC
 L192(1)SEA FILE=WPIX ABB=ON PLU=ON L189 AND (L190 OR L191)
 L193(3)SEA FILE=WPIX ABB=ON PLU=ON L189 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L194(8)SEA FILE=WPIX ABB=ON PLU=ON L189 OR L192 OR L193
 L195(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
 L196(115)SEA FILE=WPIX ABB=ON PLU=ON L195 AND (L190 OR L191)
 L197(105)SEA FILE=WPIX ABB=ON PLU=ON L196 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L198(28)SEA FILE=WPIX ABB=ON PLU=ON L197 AND ((DRY?(3A)EYE?) OR
 ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR
 ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN?
 OR ?XEROPH?)/BIX
 L199(35)SEA FILE=WPIX ABB=ON PLU=ON L194 OR L198
 L200(28)SEA FILE=WPIX ABB=ON PLU=ON L199 AND (AY<2003 OR PY<2003 OR
 PRY<2003)
 L201 24 SEA FILE=WPIX ABB=ON PLU=ON L200 AND L198

=> d que 1231

L223(1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L224 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L225(9127)SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
 L226 SEL PLU=ON L223 1- CHEM : 13 TERMS
 L227(3278)SEA FILE=MEDLINE ABB=ON PLU=ON L226
 L228(2)SEA FILE=MEDLINE ABB=ON PLU=ON L227 AND L225
 L229(32)SEA FILE=MEDLINE ABB=ON PLU=ON L227 AND L224
 L230(32)SEA FILE=MEDLINE ABB=ON PLU=ON (L228 OR L229)
 L231 11 SEA FILE=MEDLINE ABB=ON PLU=ON L230 AND PY<2003

=> d que 1273

L256(3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L257(1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L258 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L259 SEL PLU=ON L256 1- CHEM : 11 TERMS
 L260(547)SEA FILE=EMBASE ABB=ON PLU=ON L259
 L261(2325)SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT

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L262(      0)SEA FILE=EMBASE ABB=ON  PLU=ON  L260 AND L261
L263(      1)SEA FILE=EMBASE ABB=ON  PLU=ON  L260 AND L258
L264(      1)SEA FILE=EMBASE ABB=ON  PLU=ON  (L262 OR L263)
L265(      0)SEA FILE=EMBASE ABB=ON  PLU=ON  L264 AND (PY<2003 OR MY<2003)
L266(      1)SEA FILE=EMBASE ABB=ON  PLU=ON  L264 NOT L265
L267      SEL  PLU=ON  L257 1-  CHEM :      13 TERMS
L268(    2867)SEA FILE=EMBASE ABB=ON  PLU=ON  L267
L269(      2)SEA FILE=EMBASE ABB=ON  PLU=ON  L268 AND L261
L270(     24)SEA FILE=EMBASE ABB=ON  PLU=ON  L268 AND L258
L271(     24)SEA FILE=EMBASE ABB=ON  PLU=ON  (L269 OR L270)
L272(     24)SEA FILE=EMBASE ABB=ON  PLU=ON  L271 NOT L266
L273      8 SEA FILE=EMBASE ABB=ON  PLU=ON  L272 AND (PY<2003 OR MY<2003)

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=> d his 1552

(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH' ENTERED AT 07:43:51 ON 29 SEP 2005)

L552 17 SEA L541 AND L509

=> d que 1552

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L480      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
          R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
          ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
          CHRIMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L481      SEL  PLU=ON  L480 1-  CHEM :      11 TERMS
L482(    813)SEA L481
L483(      6)SEA L482 AND L480
L484(      6)DUP REM L483 (0 DUPLICATES REMOVED)
L485      SEL  PLU=ON  L480 1-  CHEM :      13 TERMS
L486(   13886)SEA L485
L487(    139)SEA L486 AND L480
L488(     88)DUP REM L487 (51 DUPLICATES REMOVED)
L489(     55)SEA FILE=BIOSIS L488
L490(     25)SEA FILE=BIOSIS L489 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L491(      6)SEA FILE=TOXCENTER L488
L492(      2)SEA FILE=TOXCENTER L491 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L493(      8)SEA FILE=PASCAL L488
L494(      2)SEA FILE=PASCAL L493 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L495(      0)SEA FILE=JICST-EPLUS L488
L496(      0)SEA FILE=JICST-EPLUS L495 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L497(      0)SEA FILE=LIFESCI L488
L498(      0)SEA FILE=LIFESCI L497 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L499(      1)SEA FILE=CANCERLIT L488
L500(      1)SEA FILE=CANCERLIT L499 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
          OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L501(     11)SEA FILE=DRUGU L488
L502(     11)SEA FILE=DRUGU L501 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
          LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?

```

OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L503(0)SEA FILE=VETU L488
 L504(0)SEA FILE=VETU L503 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L505(0)SEA FILE=VETB L488
 L506(0)SEA FILE=VETB L505 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L507(7)SEA FILE=SCISEARCH L488
 L508(3)SEA FILE=SCISEARCH L507 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L509(44)SEA L488 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
 LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
 ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L510(3)SEA FILE=BIOSIS L484
 L511(28)SEA FILE=BIOSIS L510 OR L490
 L512(0)SEA FILE=TOXCENTER L484
 L513(2)SEA FILE=TOXCENTER L512 OR L492
 L514(0)SEA FILE=PASCAL L484
 L515(2)SEA FILE=PASCAL L514 OR L494
 L516(0)SEA FILE=JICST-EPLUS L484
 L517(0)SEA FILE=JICST-EPLUS L516 OR L496
 L518(0)SEA FILE=LIFESCI L484
 L519(0)SEA FILE=LIFESCI L518 OR L498
 L520(0)SEA FILE=CANCERLIT L484
 L521(1)SEA FILE=CANCERLIT L520 OR L500
 L522(3)SEA FILE=DRUGU L484
 L523(12)SEA FILE=DRUGU L522 OR L502
 L524(0)SEA FILE=VETU L484
 L525(0)SEA FILE=VETU L524 OR L504
 L526(0)SEA FILE=VETB L484
 L527(0)SEA FILE=VETB L526 OR L506
 L528(0)SEA FILE=SCISEARCH L484
 L529(3)SEA FILE=SCISEARCH L528 OR L508
 L530(48)SEA L484 OR L509
 L531(9)SEA FILE=BIOSIS L511 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L532(0)SEA FILE=TOXCENTER L513 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L533(0)SEA FILE=PASCAL L515 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L534(0)SEA FILE=JICST-EPLUS L517 AND (AY<2003 OR PY<2003 OR PRY<2003
 OR MY<2003)
 L535(0)SEA FILE=LIFESCI L519 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L536(1)SEA FILE=CANCERLIT L521 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L537(7)SEA FILE=DRUGU L523 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L538(0)SEA FILE=VETU L525 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L539(0)SEA FILE=VETB L527 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L540(1)SEA FILE=SCISEARCH L529 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L541(18)SEA L530 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
 L542 9 SEA FILE=BIOSIS L531 AND L490
 L543(0)SEA FILE=TOXCENTER L532 AND L492

L544 (0)SEA FILE=PASCAL L533 AND L494
L545 (0)SEA FILE=JICST-EPLUS L534 AND L496
L546 (0)SEA FILE=LIFESCI L535 AND L498
L547 1 SEA FILE=CANCERLIT L536 AND L500
L548 6 SEA FILE=DRUGU L537 AND L502
L549 (0)SEA FILE=VETU L538 AND L504
L550 (0)SEA FILE=VETB L539 AND L506
L551 1 SEA FILE=SCISEARCH L540 AND L508
L552 17 SEA L541 AND L509

=> dup rem l101 l143 l201 l231 l273 l552
FILE 'HCAPLUS' ENTERED AT 07:53:36 ON 29 SEP 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'USPATFULL' ENTERED AT 07:53:36 ON 29 SEP 2005
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FILE 'USPAT2' ENTERED AT 07:53:36 ON 29 SEP 2005
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PROCESSING COMPLETED FOR L273
PROCESSING COMPLETED FOR L552

L638 94 DUP REM L101 L143 L201 L231 L273 L552 (21 DUPLICATES REMOVED)
ANSWERS '1-31' FROM FILE HCAPLUS
ANSWERS '32-52' FROM FILE USPATFULL
ANSWERS '53-76' FROM FILE WPIX
ANSWERS '77-81' FROM FILE MEDLINE
ANSWERS '82-87' FROM FILE BIOSIS
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ANSWER '94' FROM FILE SCISEARCH

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L638 ANSWER 1 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2002:414185 HCAPLUS

DOCUMENT NUMBER: 137:46034

TITLE: Protein kinase C and ERK activation are required for TFF-peptide-stimulated bronchial epithelial cell migration and tumor necrosis factor- α -induced interleukin-6 (IL-6) and IL-8 secretion

AUTHOR(S): Graness, Angela; Chwialowski, Caroline E.; Reinhold, Dirk; Thim, Lars; Hoffmann, Werner

CORPORATE SOURCE: Institut fur Molekularbiologie und Medizinische Chemie, Otto-von-Guericke-Universitat, Magdeburg, D-39120, Germany

SOURCE: Journal of Biological Chemistry (2002), 277(21), 18440-18446

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 03 Jun 2002

AB TFF-peptides (formerly P-domain peptides, trefoil factors) are typical secretory products of many mucous epithelia and are aberrantly secreted during chronic inflammatory diseases. They are known to enhance the migration of intestinal, **corneal**, and bronchial epithelial cells. Using the human bronchial epithelial cell line BEAS-2B as a model, it is shown here for the first time that TFF-peptides are capable of modulating the inflammatory response in vitro by regulating tumor necrosis factor- α -induced secretion of interleukin (IL)-6 and IL-8. In contrast, TFF2 itself does not change IL-6 and IL-8 secretion but triggers sustained activation of the extracellular signal-regulated kinases (ERK1/2) as well as phosphorylation of **c-Jun N-terminal kinase** (JNK). A complex differential regulation of tumor necrosis factor- α -induced IL-6 and IL-8 secretion by TFF2 is observed that involves signaling via protein kinase C and ERK1/2. Furthermore, the motogenic effect of TFF2 on BEAS-2B cells is analyzed using a modified Boyden chamber assay. This migratory effect is shown to be dependent not only on protein kinase C and ERK1/2 but also on the activation of the Src family of tyrosine kinases. The data presented indicate an important physiol. role of TFF-peptides during inflammatory conditions of mucous epithelia.

CC 15-10 (Immunochemistry)

Section cross-reference(s): 2, 14

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ed ab hitind hitstr 2-31

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L638 ANSWER 2 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2002:701842 HCAPLUS

DOCUMENT NUMBER: 138:103940
 TITLE: Transforming growth factor- β -induced cell death in the developing chick retina is mediated via activation of **c-jun N-terminal kinase** and downregulation of the anti-apoptotic protein Bcl-XL
 AUTHOR(S): Schuster, Norbert; Dunker, Nicole; Krieglstein, Kerstin
 CORPORATE SOURCE: Medical Faculty, Department of Anatomy and Cell Biology, University of Saarland, Homburg/Saar, D-66421, Germany
 SOURCE: Neuroscience Letters (2002), 330(3), 239-242
 CODEN: NELED5; ISSN: 0304-3940
 PUBLISHER: Elsevier Science Ireland Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 ED Entered STN: 16 Sep 2002
 AB Cell death in general and especially in neuronal cells is regulated by a complex
 interplay between survival and death signals, generated by extracellular factors like neurotrophins and intracellular regulation mechanisms. The pleiotrophic transforming growth factor- β (TGF- β) influences life and death decisions in cells depending on cell type and other growth factors present. It has been previously shown that TGF- β is necessary to induce ontogenetic cell death during retinal development. In the present study, the authors analyzed the underlying intracellular signaling processes involved in TGF- β -mediated cell death. The authors established a cell culture system mimicking the situation of ontogenetic cell death in vivo with cultured retinal cells isolated from the retinae of embryonic day 7 white leghorn chick embryos. The neutralization of TGF- β inhibits cell death of cultured retinal cells, whereas exogenous application of TGF- β is followed by enhanced apoptosis as observed by in situ cell death detection (terminal deoxynucleotidyltransferase-mediated nick end labeling) assay. TGF- β induces the activation of **c-jun N-terminal kinase** in the mitogen-activated protein kinase (MAP kinase) pathway and provokes downregulation of the anti-apoptotic BCL-XL protein. Thus, TGF- β influences cell death via activation of a pro-apoptotic MAP-kinase cascade accompanied by a downregulation of anti-apoptotic signals.
 CC 12-3 (Nonmammalian Biochemistry)
 IT Proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (Bcl-xL; TGF- β -induced cell death in developing chick retina mediation via activation of **c-jun N-terminal kinase** and downregulation of anti-apoptotic protein Bcl-XL)
 IT Apoptosis
 Embryo, animal
 (TGF- β -induced cell death in developing chick retina mediation via activation of **c-jun N-terminal kinase** and downregulation of anti-apoptotic protein Bcl-XL)
 IT Eye
 (retina; TGF- β -induced cell death in developing chick retina mediation via activation of **c-jun N-terminal kinase** and downregulation of anti-apoptotic protein Bcl-XL)
 IT Transforming growth factors
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (β -; TGF- β -induced cell death in developing chick retina

mediation via activation of **c-jun N-terminal kinase** and downregulation of anti-apoptotic protein Bcl-XL)

IT 155215-87-5, **c-Jun N-terminal kinase**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(TGF- β -induced cell death in developing chick retina mediation via activation of **c-jun N-terminal kinase** and downregulation of anti-apoptotic protein Bcl-XL)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 3 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 7

ACCESSION NUMBER: 2001:712259 HCAPLUS

DOCUMENT NUMBER: 135:341703

TITLE: The Rac GTPase-activating protein RotundRacGAP interferes with Drac1 and Dcdc42 signaling in *Drosophila melanogaster*

AUTHOR(S): Raymond, Karine; Bergeret, Evelyne; Dagher, Marie-Claire; Breton, Rock; Griffin-Shea, Ruth; Fauvarque, Marie-Odile

CORPORATE SOURCE: Departement de Biologie Moleculaire et Structurale, CEA-CNRS-UJF, UMR 5092, Grenoble, 38054, Fr.

SOURCE: Journal of Biological Chemistry (2001), 276(38), 35909-35916

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 28 Sep 2001

AB RhoGTPases are neg. regulated by GTPase-activating proteins (GAPs). Here *Drosophila* RotundRacGAP is active in vitro on Drac1 and Dcdc42 but not Drh1. Similarly, in yeast, RotundRacGAP interacts specifically with Drac1 and Dcdc42, as well as with their activated V12 forms, showing a particularly strong interaction with Dcdc42V12. In the fly, lowering RotundRacGAP dosage specifically modifies eye defects induced by expressing Drac1 or Dcdc42 but not Drh1, confirming that Drac1 and Dcdc42 are indeed in vivo targets of RotundRacGAP. Furthermore, embryonic-directed expression of either RotundRacGAP, or dominant neg. Drac1N17, transgenes induces similar defects in dorsal closure and inhibits Drac1-dependent cytoskeleton assembly at the leading edge. Expression of truncated forms of RotundRacGAP shows that the GAP domain of RotundRacGAP is essential for its function. Unexpectedly, transgenes encoding Drac1N17, Dcdc42N17, or RotundRacGAP do not affect the **c-Jun N-terminal kinase**-dependent gene expression of decapentaplegic and puckered, indicating that another Drac1-independent signal redundantly activates this pathway. Finally, in a situation where Drac1 is constitutively activated, RotundRacGAP greatly reduces the ectopic expression of decapentaplegic, possibly by neg. regulating Dcdc42.

CC 12-3 (Nonmammalian Biochemistry)

IT Cytoskeleton
Drosophila melanogaster

Eye

Signal transduction, biological

(the Rac GTPase-activating protein RotundRacGAP interferes with Drac1 and Dcdc42 signaling in *Drosophila melanogaster*)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 4 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 8

ACCESSION NUMBER: 2001:500948 HCAPLUS

DOCUMENT NUMBER: 135:193763

TITLE: **c-Jun N-terminal**

kinase activation is required for the inhibition of neovascularization by thrombospondin-1

AUTHOR(S): Jimenez, Benilde; Volpert, Olga V.; Reiher, Frank; Chang, Lufen; Munoz, Alberto; Karin, Michael; Bouck, Noel

CORPORATE SOURCE: Departamento de Bioquimica, Facultad de Medicina, Universidad Autonoma de Madrid, Madrid, Spain

SOURCE: Oncogene (2001), 20(26), 3443-3448

CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 12 Jul 2001

AB Thrombospondin-1 (TSP-1) is a potent inhibitor of angiogenesis that acts directly on endothelial cells via the CD36 surface receptor mol. to halt their migration, proliferation, and morphogenesis in vitro and to block neovascularization in vivo. Here the authors show that inhibitory signals elicited by TSP-1 did not alter the ability of inducers of angiogenesis to activate p42 and p44 mitogen-activated protein kinase (MAPK). Rather, TSP-1 induced a rapid and transient activation of **c-Jun N-terminal kinases** (JNK). JNK activation by TSP-1 required engagement of CD36, as it was blocked by antagonistic CD36 antibodies and stimulated by short anti-angiogenic peptides derived from TSP-1 that act exclusively via CD36. TSP-1 inhibition of **corneal** neovascularization induced by bFGF was severely impaired in mice null for JNK-1, pointing to a critical role for this stress-activated kinase in the inhibition of neovascularization by TSP-1.

CC 14-5 (Mammalian Pathological Biochemistry)

IT Thrombospondins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(1; **c-Jun N-terminal**

kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT Signal transduction, biological

(**c-Jun N-terminal**

kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT Eye

(cornea, neovascularization; **c-Jun N-terminal kinase** activation

is required for inhibition of neovascularization by thrombospondin-1)

IT Blood vessel

(endothelium; **c-Jun N-terminal**

kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT CD36 (antigen)

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(in **c-Jun N-terminal**

kinase activation in inhibition of neovascularization by thrombospondin-1)

IT Angiogenesis

(neovascularization; **c-Jun N-**

terminal kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT 155215-87-5, c-Jun N-terminal kinase 289898-51-7, JNK-1
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (c-Jun N-terminal kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT 137632-07-6, p44 MAP kinase 137632-08-7, p42 MAP kinase
 RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
 (c-Jun N-terminal kinase activation is required for inhibition of neovascularization by thrombospondin-1 in relation to)

IT 106096-93-9, Basic fibroblast growth factor
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (neovascularization induced by; c-Jun N-terminal kinase activation is required for inhibition of neovascularization by thrombospondin-1)

IT 289898-51-7, JNK-1
 RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (c-Jun N-terminal kinase activation is required for inhibition of neovascularization by thrombospondin-1)

RN 289898-51-7 HCAPLUS
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 5 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2000:290752 HCAPLUS

DOCUMENT NUMBER: 133:56243

TITLE: TAK1 participates in c-Jun N-terminal kinase

signaling during Drosophila development

AUTHOR(S): Takatsu, Yoshihiro; Nakamura, Makoto; Stapleton, Mark; Danos, Maria C.; Matsumoto, Kunihiro; O'Connor, Michael B.; Shibuya, Hiroshi; Ueno, Naoto

CORPORATE SOURCE: Division of Morphogenesis, Department of Developmental Biology, National Institute for Basic Biology, Okazaki, 444-8585, Japan

SOURCE: Molecular and Cellular Biology (2000), 20(9), 3015-3026

CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 05 May 2000

AB We isolated a Drosophila homolog of TAK1 (dTAK1) which contains an extensively conserved N-terminal kinase domain and a partially conserved

C-terminal domain. To learn about possible endogenous roles of TAK1 during animal development, we generated transgenic flies which express dTAK1 or the mouse TAK1 (mTAK1) gene in the fly visual system. Ectopic activation of TAK1 signaling leads to a small **eye** phenotype, and genetic anal. reveals that this phenotype is a result of ectopically induced apoptosis. Genetic and biochem. analyses also indicate that the **c-Jun N-terminal kinase**

(JNK) signaling pathway is specifically activated by TAK1 signaling. Expression of a dominant neg. form of dTAK during embryonic development resulted in various embryonic cuticle defects including dorsal open phenotypes. Our results strongly suggest that in *D. melanogaster*, TAK1 functions as a MAPKKK in the JNK signaling pathway and participates in such diverse roles as control of cell shape and regulation of apoptosis.

CC 12-3 (Nonmammalian Biochemistry)

Section cross-reference(s): 3, 7

IT Apoptosis

Cell morphology

Development, nonmammalian postembryonic

Drosophila melanogaster

Eye

Molecular cloning

Protein sequences

Signal transduction, biological

cDNA sequences

(TGFβ-activated kinase sequence and role in c-

Jun N-terminal kinase signaling

during *Drosophila* development)

IT Invertebrate body covering

(cuticle; TGFβ-activated kinase sequence and role in c-

Jun N-terminal kinase signaling

during *Drosophila* development)

IT Embryo, animal

(embryogenesis; TGFβ-activated kinase sequence and role in

c-Jun N-terminal kinase

signaling during *Drosophila* development)

IT 146702-84-3, TGF-β activated-kinase 1

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(TGFβ-activated kinase sequence and role in c-

Jun N-terminal kinase signaling

during *Drosophila* development)

IT 155215-87-5, **c-Jun N-terminal**

kinase

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(TGFβ-activated kinase sequence and role in c-

Jun N-terminal kinase signaling

during *Drosophila* development)

IT 263118-03-2

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(amino acid sequence; TGFβ-activated kinase sequence and role in

c-Jun N-terminal kinase

signaling during *Drosophila* development)

IT 247316-10-5, GenBank AF199466

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(nucleotide sequence; TGF β -activated kinase sequence and role in
c-Jun N-terminal kinase
signaling during *Drosophila* development)

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 6 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 1999:632643 HCAPLUS

DOCUMENT NUMBER: 131:349230

TITLE: De novo synthesis of sphingolipids is required for
cell survival by down-regulating **c-**
Jun N-terminal

kinase in *Drosophila* imaginal discs

AUTHOR(S): Adachi-Yamada, Takashi; Gotoh, Tomokazu; Sugimura,
Isamu; Tateno, Minoru; Nishida, Yasuyoshi; Onuki,
Tomoya; Date, Hideyuki

CORPORATE SOURCE: Division of Biological Science, Graduate School of
Science, Nagoya University, Nagoya, 464-8602, Japan

SOURCE: Molecular and Cellular Biology (1999),

19(10), 7276-7286

CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 06 Oct 1999

AB Mitogen-activated protein kinase (MAPK) is a conserved eukaryotic
signaling factor that mediates various signals, cumulating in the
activation of transcription factors. Extracellular signal-regulated
kinase (ERK), a MAPK, is activated through phosphorylation by the kinase
MAPK/ERK kinase (MEK). To elucidate the extent of the involvement of ERK
in various aspects of animal development, we searched for a *Drosophila*
mutant which responds to elevated MEK activity and herein identified a
lace mutant. Mutants with mild lace alleles grow to become adults with
multiple aberrant morphologies in the appendages, compound **eye**,
and bristles. These aberrations were suppressed by elevated MEK activity.
Structural and transgenic analyses of the lace cDNA have revealed that the
lace gene product is a membrane protein similar to the yeast protein LCB2,
a subunit of serine palmitoyltransferase (SPT), which catalyzes the 1st
step of sphingolipid biosynthesis. In fact, SPT activity in the fly
expressing epitope-tagged Lace was absorbed by epitope-specific antibody.
The number of dead cells in various imaginal disks of a lace hypomorph was
considerably increased, thereby ectopically activating **c-**
Jun N-terminal kinase (JNK), another
MAPK. These results account for the adult phenotypes of the lace mutant
and suppression of the phenotypes by elevated MEK activity: we hypothesize
that mutation of lace causes decreased de novo synthesis of sphingolipid
metabolites, some of which are signaling mols., and ≥ 1 of these
changes activates JNK to elicit apoptosis. The ERK pathway may be
antagonistic to the JNK pathway in the control of cell survival.

CC 12-3 (Nonmammalian Biochemistry)

Section cross-reference(s): 3, 7

IT Nervous system

(antenna; sphingolipid formation is required for cell survival by
down-regulating **c-Jun N-terminal**
kinase in *Drosophila* imaginal disks)

IT **Eye**

(compound; sphingolipid formation is required for cell survival by
down-regulating **c-Jun N-terminal**

- kinase in Drosophila imaginal disks)**
- IT Embryo, animal
(embryogenesis; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Animal tissue
(imaginal disk; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(lance; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Phosphorylation, biological
(protein; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Organ, animal
(sensory, bristle; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Apoptosis
Development, nonmammalian postembryonic
Drosophila melanogaster
Leg
Protein sequences
Salivary gland
Signal transduction, biological
Wing, anatomical
cDNA sequences
(sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT Sphingolipids
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT 250292-32-1
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(amino acid sequence; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT 237999-82-5, GenBank AB017359
RL: PRP (Properties)
(nucleotide sequence; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase in Drosophila imaginal disks)**
- IT 142243-02-5, Mitogen-activated protein kinase 142805-58-1, MAPK/ERK kinase 155215-87-5, **c-Jun N-terminal kinase**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological

occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process) (sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase** in *Drosophila* imaginal disks)

IT 62213-50-7, Serine palmitoyltransferase

RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)

(subunit LCB2; sphingolipid formation is required for cell survival by down-regulating **c-Jun N-terminal kinase** in *Drosophila* imaginal disks)

REFERENCE COUNT: 104 THERE ARE 104 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 7 OF '94 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 1998:582641 HCAPLUS

DOCUMENT NUMBER: 129:270880

TITLE: Endogenous FGF1-induced activation and synthesis of extracellular signal-regulated kinase 2 reduce cell apoptosis in retinal-pigmented epithelial cells

AUTHOR(S): Guillonneau, Xavier; Bryckaert, Marijke; Launay-Longo, Catherine; Courtois, Yves; Mascarelli, Frederic
CORPORATE SOURCE: Developpement, Vieillissement et Pathologie de la Retine, INSERM U. 450, Affiliee CNRS, Paris, 75016, Fr.

SOURCE: Journal of Biological Chemistry (1998), 273(35), 22367-22373

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 14 Sep 1998

AB Retinal-pigmented epithelial (RPE) cell survival is critical to the maintenance of the function of the neural retinal and in the development of various retina degenerations. We investigated mol. mechanisms involved in this function by assessing apoptosis in RPE cells following serum deprivation. Apoptosis induced by serum withdrawal is lower in aged RPE cells because of higher endogenous acidic fibroblast growth factor (FGF1) synthesis and secretion. These expts. examined several aspects of FGF signaling and the contribution of endogenous FGF1 to activation of the extracellular signal-regulated kinase 2 (ERK2). In aged RPE cells, FGFR1 was rapidly activated, and its autophosphorylation followed the kinetics of endogenous FGF1 secretion, before the onset of apoptosis. ERK2 phosphorylation, activity, and de novo synthesis increased at the same time. In marked contrast, no de novo **JNK1** synthesis was observed. MEK1 inhibition resulted in lower levels of ERK2 activation and synthesis and higher levels of apoptosis. Treatment with neutralizing anti-FGF1 or blocking anti-FGFR1 antibodies mimics these effects. Thus, this study strongly suggests that the survival-increasing effect of FGF1 in aged RPE cells is because of an autocrine/paracrine loop in which the ERK2 cascade plays a pivotal role.

CC 2-5 (Mammalian Hormones)

IT Eye

(pigment epithelium; FGF-1-induced activation and synthesis of ERK2 kinase reducing apoptosis in retinal-pigmented epithelial cells and signaling therefor)

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 8 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:120572 HCAPLUS

DOCUMENT NUMBER: 140:157431

TITLE: Antisense oligonucleotides for inhibition of c-jun protein N-terminal kinase mRNA for treatment of prostate cancer, inflammation and fibrotic diseases

INVENTOR(S): McKay, Robert; Dean, Nicholas M.; Monia, Brett P.; Nero, Pamela S.; Gaarde, William A.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 71 pp., Cont.-in-part of U.S. Ser. No. 774,809.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004029823	A1	20040212	US 2003-345444	20030115 <--
US 5877309	A	19990302	US 1997-910629	19970813 <--
US 6221850	B1	20010424	US 1998-130616	19980807 <--
US 6133246	A	20001017	US 1999-287796	19990407 <--
US 2003004120	A1	20030102	US 2001-774809	20010131 <--
US 6809193	B2	20041026		

PRIORITY APPLN. INFO.: US 1997-910629 A2 19970813 <--
US 1998-130616 A2 19980807 <--
US 1999-287796 A2 19990407 <--
US 1999-396902 B2 19990915 <--
US 2001-774809 A2 20010131 <--

ED Entered STN: 13 Feb 2004

AB The present invention relates to antisense oligonucleotides for inhibition of c-jun protein N-terminal kinase mRNA for treatment of prostate cancer, inflammation and fibrotic diseases. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other JNK proteins and specific isoforms thereof.

IC ICM A61K048-00

ICS C07H021-04

INCL 514044000; 536023200

CC 1-6 (Pharmacology)

Section cross-reference(s): 3

IT Eye

(conjunctiva, scarring; antisense oligonucleotides for inhibition of c-jun protein N-terminal kinase mRNA for treatment of prostate cancer, inflammation and fibrotic diseases)

IT 155215-87-5 289898-51-7, Jun N-terminal kinase 1 289899-93-0, Jun N-terminal kinase 2

RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)

(antisense oligonucleotides for inhibition of c-jun protein N-terminal kinase mRNA for treatment of prostate cancer, inflammation and fibrotic diseases)

IT 289898-51-7, Jun N-terminal kinase 1

RL: ADV (Adverse effect, including toxicity); BSU (Biological study,

unclassified); BIOL (Biological study)
 (antisense oligonucleotides for inhibition of c-jun protein N-terminal
 kinase mRNA for treatment of prostate cancer, inflammation and fibrotic
 diseases)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L638 ANSWER 9 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:472319 HCAPLUS

DOCUMENT NUMBER: 141:47322

TITLE: Sulfur heterocycle-condensed pyrimidinedione
 derivatives, prodrugs of them, JNK inhibitors
 containing them, and pharmaceuticals containing them

INVENTOR(S): Ito, Fumio; Kimura, Hiroyuki; Ikata, Hideki; Kitamura,
 Shuji; Kawamoto, Tomohiro; Abe, Hidenori

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 117 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004161716	A2	20040610	JP 2002-332027	20021115 <--
PRIORITY APPLN. INFO.:			JP 2002-332027	20021115 <--

OTHER SOURCE(S): MARPAT 141:47322

ED Entered STN: 11 Jun 2004

AB The derivs., useful for prevention and treatment of diseases involving
 JNK, e.g. cardiac failure, hypertension, rheumatoid arthritis, asthma,
 Alzheimer's disease, ischemia, etc., are represented by I [R = H,
 (un)substituted hydrocarbyl, (un)substituted heterocyclyl; X1, X2 =
 (un)substituted C2-4 alkylene; X3 = direct bond, (un)substituted C1-5
 alkylene, (un)substituted C2-4 alkenylene; Y = direct bond,
 (un)substituted divalent cyclic group; Q = direct bond, O, S, NR1 [R1 = H,
 (un)substituted lower alkyl]; L = direct bond, CONR2 [R2 = H,
 (un)substituted lower alkyl]; ring A = (un)substituted N-heterocycle; n =
 0, 1, 2]. JNK inhibitors contain I, their salts, or prodrugs of I. Thus,
 IC50 of 4-(6-aminopyridin-3-yl)-N-[3-(1,1,6,8-tetraoxo-9-phenyl-1,3,4,8-
 tetrahydro-2H-1λ6-pyrimido[6,1-b][1,3]thiazin-7-yl)propyl]benzamide
 hydrochloride (II preparation given) against human JNK1 was 0.00082
 μM. Capsules and tablets containing II were also formulated.

IC ICM C07D513-04

ICS A61K031-542; A61P001-04; A61P001-16; A61P003-10; A61P007-08;
 A61P009-00; A61P009-04; A61P009-10; A61P009-12; A61P009-14;
 A61P011-00; A61P011-06; A61P013-12; A61P017-00; A61P017-04;
 A61P017-06; A61P019-02; A61P019-06; A61P021-04

CC 1-8 (Pharmacology)

Section cross-reference(s): 28, 63

IT Eye, disease

(diabetic retinopathy, prevention and treatment of;
 preparation of sulfur heterocycle-condensed pyrimidinedione derivs. as JNK
 inhibitors)

L638 ANSWER 10 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:1006981 HCAPLUS

DOCUMENT NUMBER: 140:42182
 TITLE: Preparation of cyanomethylidene-substituted azoles and their use as protein kinase modulators
 INVENTOR(S): Gaillard, Pascale; Gotteland, Jean-Pierre; Jeanclaude-Etter, Isabelle; Schwarz, Matthias; Thomas, Russel J.
 PATENT ASSIGNEE(S): Applied Research Systems ARS Holding N.V., Neth. Antilles
 SOURCE: PCT Int. Appl., 199 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003106455	A1	20031224	WO 2003-EP50225	20030613 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2487948	AA	20031224	CA 2003-2487948	20030613 <--
EP 1527070	A1	20050504	EP 2003-759982	20030613 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			EP 2002-100710	A 20020614 <--
			WO 2003-EP50225	W 20030613

OTHER SOURCE(S): MARPAT 140:42182

ED Entered STN: 26 Dec 2003

AB The present invention is related to cyanomethylidene-substituted azoles (shown as I; variables defined below; e.g. (2-chloropyrimidin-4-yl)(4-ethyl-3H-thiazol-2-ylidene)acetonitrile) notably for use as pharmaceutically active compds., as well as to pharmaceutical formulations containing such azole derivs. Said azole derivs. are modulators of the protein kinase signaling pathways, particularly the one involving **c-Jun N-terminal kinase** and/or glycogen kinase synthase 3. The present invention is furthermore related to novel azole derivs. as well as to methods of their preparation X is O, S or NR0, with R0 being H or an (un)substituted C1-C6 alkyl; A is 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl group; addnl. details are given in the claims. IC50 values are tabulated for inhibition of JNK-3 and GSK3 β by several examples of I. Methods of preparation are claimed and example prepns. of 31 intermediates and 189 title compds. are included. For example, (2-chloropyrimidin-4-yl)(4-ethyl-3H-thiazol-2-ylidene)acetonitrile was prepared in 85.5 % yield from (4-ethyl-1,3-thiazol-2-yl)acetonitrile, 2,4-dichloropyrimidine and LiH in THF; the reactant (4-ethyl-1,3-thiazol-2-yl)acetonitrile was prepared in 81 % yield from 1-bromo-2-butanone, 2-cyanothioacetamide and Et3N in EtOH.

IC ICM C07D417-06

ICS C07D417-14; A61K031-506; A61K031-53; A61P003-10

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 63

IT Alzheimer's disease

Anti-Alzheimer's agents
 Anti-inflammatory agents
 Anti-ischemic agents
 Antiartherosclerotics
 Antiarthritics
 Antiasthmatics
 Anticonvulsants
 Antiglaucoma agents
 Antiobesity agents
 Antiparkinsonian agents
 Antirheumatic agents
 Antitumor agents
 Arteriosclerosis
 Arthritis
 Asthma
 Cardiovascular agents
 Cardiovascular system, disease
 Drug delivery systems
 Epilepsy
 Glaucoma (disease)
 Human
 Inflammation
 Ischemia
 Multiple sclerosis
 Neoplasm
 Nerve, disease
 Nervous system agents
 Obesity
 Parkinson's disease
 Rheumatoid arthritis
 Transplant rejection
 (preparation of cyanomethylidene-substituted azoles and their use as protein
 kinase modulators)

IT **Eye, disease**

(retinopathy; preparation of cyanomethylidene-substituted azoles
 and their use as protein kinase modulators)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 11 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:796705 HCAPLUS

DOCUMENT NUMBER: 139:307750

TITLE: Preparation of 7-azaindoles as inhibitors of c
 -Jun N-terminal
 kinases

INVENTOR(S): Graczyk, Piotr; Numata, Hirotoshi; Bhatia, Gurpreet;
 Medland, Darren Peter

PATENT ASSIGNEE(S): Eisai London Research Laboratories Limited, UK

SOURCE: PCT Int. Appl., 44 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	---	-----	-----	-----
WO 2003082869	A1	20031009	WO 2003-GB1115	20030317 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
 PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
 TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
 KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
 FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 CA 2479205 AA 20031009 CA 2003-2479205 20030317 <--
 EP 1490365 A1 20041229 EP 2003-709986 20030317 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 PRIORITY APPLN. INFO.: GB 2002-7488 A 20020328 <--
 GB 2003-400 A 20030108
 WO 2003-GB1115 W 20030317

OTHER SOURCE(S): MARPAT 139:307750

ED Entered STN: 10 Oct 2003

AB The title compds. I [where R = (un)substituted cyclohydrocarbyl or heterocyclyl] and pharmaceutically acceptable salts, esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents, or prodrugs thereof are prepared as inhibitors of **c-Jun N-terminal kinases** (JNK). I are useful for the treatment of neurodegenerative disorders related to apoptosis and/or inflammation (no data). For example, 7-aza-5-(2-thienyl)indole (II) was prepared in a multi-step synthesis. II showed IC50 of <0.5 μ M against JNK3.

IC ICM C07D471-04

ICS A61P025-00; A61K031-437

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT Inflammation

(Crohn's disease; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Intestine, disease

(Crohn's; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Nervous system, disease

(Guillain-Barre syndrome; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Nervous system, disease

(Huntington's chorea, senile; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Apoptosis

(Neuronal; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Inflammation

Pancreas, disease

(acute pancreatitis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Pain

(acute; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Platelet (blood)

(aggregation, thrombin induced; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Nervous system, disease

(amyotrophic lateral sclerosis; preparation of azaindoles as inhibitors of

c-jun N-terminal kinases
)
 IT Dermatitis
 (atopic; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Heart, disease
 (attack; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Autoimmune disease
 Inflammation
 Stomach, disease
 (autoimmune gastritis; preparation of azaindoles as inhibitors of c
 -jun N-terminal kinases)
 IT Anemia (disease)
 Autoimmune disease
 (autoimmune hemolytic anemia; preparation of azaindoles as inhibitors of
 c-jun N-terminal kinases
)
 IT Autoimmune disease
 Inflammation
 Thyroid gland, disease
 (autoimmune thyroiditis; preparation of azaindoles as inhibitors of
 c-jun N-terminal kinases
)
 IT Bronchi, disease
 Inflammation
 (bronchitis; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases)
 IT Hypertrophy
 (cardiac; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Ischemia
 (cerebral; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases)
 IT Infection
 (chronic active hepatitis; preparation of azaindoles as inhibitors of
 c-jun N-terminal kinases
)
 IT Inflammation
 Pancreas, disease
 (chronic pancreatitis; preparation of azaindoles as inhibitors of c
 -jun N-terminal kinases)
 IT Pain
 (chronic; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Nerve, disease
 (death; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Nerve, disease
 (degeneration, hypoxia-related; preparation of azaindoles as inhibitors of
 c-jun N-terminal kinases
)
 IT Nervous system, disease
 (degeneration; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases)
 IT Mental disorder
 (dementia, olivopontocerebellar, cerebrovascular, in HIV-infected
 patient; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases)
 IT Nerve, disease

(demyelination; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Bone, disease
(destructive; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Platelet (blood)
(disease, thrombocytopenia; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Angiogenic factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(disorder; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Anti-inflammatory agents
(drug containing; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endoperoxidase synthase-2; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Kidney, disease
(failure; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Neurotoxicity
Toxicity
(glutamate; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Injury
(head, traumatic; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Heart, disease
(hypertrophy; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Inflammation
Kidney, disease
(immune complex glomerulonephritis; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Intestine, disease
(inflammatory; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Head, disease
(injury, traumatic; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Reperfusion
(injury; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Brain, disease
(ischemia; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Brain, disease
(metachromatic leukodystrophy; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT Cell death

(neuron; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Mental disorder
(neurosis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Agranulocytosis
(neutropenia, autoimmune; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Hypoxia
(organ, acute; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p38, drug containing; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Artery, disease
Inflammation
(periarteritis nodosa; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Nerve, disease
(peripheral neuropathy; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT Nerve, disease
(polyneuropathy, acute or chronic inflammatory; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

IT AIDS (disease)
Allergy
Allergy inhibitors
Alzheimer's disease
Amyloidosis
Analgesics
Angiogenesis inhibitors
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Asthma
Autoimmune disease
Diabetes mellitus
Epilepsy
Graves' disease
Human
Hypoglycemia
Immunomodulators
Infection
Inflammation
Lyme disease
Meningitis
Multiple sclerosis
Myasthenia gravis
Neoplasm
Parkinson's disease
Psoriasis

Rheumatoid arthritis

Seizures

Sjogren's syndrome

(preparation of azaindoles as inhibitors of c-jun

N-terminal kinases)

IT Drug delivery systems

(prodrugs; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Disease, animal

(proliferative; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Injury

(reperfusion; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Connective tissue, disease

(scleroderma; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Lupus erythematosus

(systemic; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Blood, disease

(thrombocytopenia; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Head, disease

Spinal cord, disease

(trauma; preparation of azaindoles as inhibitors of c-jun

N-terminal kinases)

IT Inflammation

Intestine, disease

(ulcerative colitis; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Hyperplasia

(vascular; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT Hepatitis

(viral, chronic active; preparation of azaindoles as inhibitors of c-

-jun N-terminal kinases)

IT 344454-28-0P 611204-92-3P 611204-93-4P 611204-94-5P 611204-95-6P

611204-96-7P 611204-97-8P 611204-98-9P 611204-99-0P 611205-00-6P

611205-01-7P 611205-02-8P 611205-03-9P 611205-04-0P 611205-05-1P

611205-06-2P 611205-07-3P 611205-08-4P 611205-09-5P 611205-10-8P

611205-11-9P 611205-12-0P 611205-13-1P 611205-14-2P 611205-15-3P

611205-16-4P 611205-17-5P 611205-18-6P 611205-19-7P 611205-20-0P

611205-21-1P 611205-22-2P 611205-23-3P 611205-24-4P 611205-25-5P

611205-26-6P 611205-27-7P 611205-28-8P 611205-29-9P 611205-30-2P

611205-31-3P 611205-32-4P 611205-33-5P 611205-34-6P 611205-35-7P

611205-36-8P 611205-37-9P 611205-38-0P 611205-39-1P 611205-40-4P

611205-41-5P 611205-42-6P 611205-43-7P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU

(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

(Uses)

(drug candidate; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT 155215-87-5, JNK 291756-39-3, JNK3

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitor; preparation of azaindoles as inhibitors of c-

jun N-terminal kinases)

IT 113423-51-1P 183208-32-4P 183208-34-6P 611204-90-1P 611204-91-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)

(intermediate; preparation of azaindoles as inhibitors of c-jun N-terminal kinases)

IT 271-63-6, 7-Azaindole 768-35-4, 3-Fluorophenylboronic acid

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of azaindoles as inhibitors of c-jun

N-terminal kinases)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 12 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:796704 HCAPLUS

DOCUMENT NUMBER: 139:307749

TITLE: Preparation of 7-azaindoles as inhibitors of c-jun N-terminal

kinases for treatment of neurodegenerative disorders

INVENTOR(S): Graczyk, Piotr; Numata, Hirotooshi; Khan, Afzal; Palmer, Vanessa

PATENT ASSIGNEE(S): Eisai London Research Laboratories Limited, UK

SOURCE: PCT Int. Appl., 70 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003082868	A1	20031009	WO 2003-GB1112	20030317 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2480317	AA	20031009	CA 2003-2480317	20030317 <--
EP 1490364	A1	20041229	EP 2003-709984	20030317 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRIORITY APPLN. INFO.:			GB 2002-7491	A 20020328 <--
			GB 2002-17330	A 20020725 <--
			WO 2003-GB1112	W 20030317

OTHER SOURCE(S): MARPAT 139:307749

ED Entered STN: 10 Oct 2003

AB The title compds. I [wherein R = (un)substituted cyclohydrocarbyl or heterocyclyl; R' = (un)substituted alkyl, alkenyl, alkynyl, cyclohydrocarbyl, or heterocyclyl; R'' = H, (un)substituted alkyl, cyclohydrocarbyl, or heterocyclyl; X = O, S, (un)substituted NH, or alkylene; Y = a single bond, O, (un)substituted NH, or alkylene; Z = O, S, or (un)substituted NH] and pharmaceutically acceptable salts, esters, amides, carbamates, carbonates, ureides, solvates, hydrates, affinity reagents, or prodrugs thereof are prepared as inhibitors of c-Jun N-terminal kinases (JNK), and are useful for the treatment of neurodegenerative disorders related to apoptosis and/or inflammation (no data). For example, the compound II was prepared in a multi-step synthesis. II showed IC50 of 0.52 μ M against

JNK3 kinase.

IC ICM C07D471-04
ICS A61K031-437; A61P025-16; A61P025-28

CC 28-2 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT Inflammation
(Crohn's disease; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Intestine, disease
(Crohn's; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nervous system, disease
(Guillain-Barre syndrome; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nervous system, disease
(Huntington's chorea, senile; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Apoptosis
(Neuronal; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Inflammation
Pancreas, disease
(acute pancreatitis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Pain
(acute; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Platelet (blood)
(aggregation, thrombin induced; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nervous system, disease
(amyotrophic lateral sclerosis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Dermatitis
(atopic; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Heart, disease
(attack; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Autoimmune disease
Inflammation
Stomach, disease
(autoimmune gastritis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Anemia (disease)
Autoimmune disease
(autoimmune hemolytic anemia; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**)

for treatment of neurodegenerative disorders)

IT Autoimmune disease
Inflammation
Thyroid gland, disease
(autoimmune thyroiditis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Bronchi, disease
Inflammation
(bronchitis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Hypertrophy
(cardiac; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Ischemia
(cerebral; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Infection
(chronic active hepatitis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Inflammation
Pancreas, disease
(chronic pancreatitis; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Pain
(chronic; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nerve, disease
(death; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nerve, disease
(degeneration, hypoxia-related; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nervous system, disease
(degeneration; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Mental disorder
(dementia, olivopontocerebellar, cerebrovascular, in HIV-infected patient; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Nerve, disease
(demyelination; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Bone, disease
(destructive; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)

IT Platelet (blood)
(disease, thrombocytopenia; preparation of azaindoles as inhibitors of

- c-jun N-terminal kinases**
for treatment of neurodegenerative disorders)
- IT Angiogenic factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(disorder; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Anti-inflammatory agents
(drug containing; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Prostaglandins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(endoperoxidase synthase-2; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**
for treatment of neurodegenerative disorders)
- IT Kidney, disease
(failure; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of
neurodegenerative disorders)
- IT Neurotoxicity
Toxicity
(glutamate; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases**
for treatment of neurodegenerative disorders)
- IT Injury
(head, traumatic; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Heart, disease
(hypertrophy; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Inflammation
Kidney, disease
(immune complex glomerulonephritis; preparation of azaindoles as inhibitors
of **c-jun N-terminal kinases** for treatment of neurodegenerative disorders)
- IT Intestine, disease
(inflammatory; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Head, disease
(injury, traumatic; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Reperfusion
(injury; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for treatment of
neurodegenerative disorders)
- IT Brain, disease
(ischemia; preparation of azaindoles as inhibitors of **c-jun N-terminal kinases** for
treatment of neurodegenerative disorders)
- IT Brain, disease
(metachromatic leukodystrophy; preparation of azaindoles as inhibitors of

c-jun N-terminal kinases
 for treatment of neurodegenerative disorders)

IT Cell death
 (neuron; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases for treatment of
 neurodegenerative disorders)

IT Mental disorder
 (neurosis; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT Agranulocytosis
 (neutropenia, autoimmune; preparation of azaindoles as inhibitors of
 c-jun N-terminal kinases
 for treatment of neurodegenerative disorders)

IT Hypoxia
 (organ, acute; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT Proteins
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (p38, drug containing; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT Artery, disease
 Inflammation
 (periarteritis nodosa; preparation of azaindoles as inhibitors of c
 -jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT Nerve, disease
 (peripheral neuropathy; preparation of azaindoles as inhibitors of c
 -jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT Nerve, disease
 (polyneuropathy, acute or chronic inflammatory; preparation of azaindoles as
 inhibitors of c-jun N-terminal
 kinases for treatment of neurodegenerative disorders)

IT AIDS (disease)
 Allergy
 Allergy inhibitors
 Alzheimer's disease
 Amyloidosis
 Analgesics
 Angiogenesis inhibitors
 Anti-AIDS agents
 Anti-Alzheimer's agents
 Anti-infective agents
 Antiasthmatics
 Anticonvulsants
 Antidiabetic agents
 Antiparkinsonian agents
 Antirheumatic agents
 Antitumor agents
 Asthma
 Autoimmune disease
 Diabetes mellitus
 Epilepsy
 Graves' disease
 Human
 Hypoglycemia
 Immunomodulators

Infection
 Inflammation
 Lyme disease
 Meningitis
 Multiple sclerosis
 Myasthenia gravis
 Neoplasm
 Parkinson's disease
 Psoriasis
 Rheumatoid arthritis
 Seizures

Sjogren's syndrome

(preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases for treatment of
 neurodegenerative disorders)

- IT Drug delivery systems
 (prodrugs; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Disease, animal
 (proliferative; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Injury
 (reperfusion; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Connective tissue, disease
 (scleroderma; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Lupus erythematosus
 (systemic; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Blood, disease
 (thrombocytopenia; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Head, disease
 Spinal cord, disease
 (trauma; preparation of azaindoles as inhibitors of c-jun
 N-terminal kinases for treatment of
 neurodegenerative disorders)
- IT Inflammation
 Intestine, disease
 (ulcerative colitis; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Hyperplasia
 (vascular; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT Hepatitis
 (viral, chronic active; preparation of azaindoles as inhibitors of c-
 jun N-terminal kinases for
 treatment of neurodegenerative disorders)
- IT 344454-28-0P 611204-93-4P 611204-95-6P 611204-96-7P 611204-97-8P
 611204-98-9P 611204-99-0P 611205-00-6P 611205-01-7P 611205-02-8P
 611205-03-9P 611205-04-0P 611205-05-1P 611205-06-2P 611205-07-3P

611205-08-4P 611205-09-5P 611205-10-8P 611205-11-9P 611205-12-0P
 611205-13-1P 611205-14-2P 611226-91-6P 611226-94-9P 611226-95-0P
 611226-96-1P 611226-97-2P 611226-98-3P 611226-99-4P 611227-00-0P
 611227-01-1P 611227-02-2P 611227-03-3P 611227-04-4P 611227-05-5P
 611227-06-6P 611227-07-7P 611227-08-8P 611227-09-9P 611227-10-2P
 611227-11-3P 611227-12-4P 611227-13-5P 611227-14-6P 611227-15-7P
 611227-16-8P 611227-17-9P 611227-18-0P 611227-19-1P 611227-20-4P
 611227-21-5P 611227-22-6P 611227-23-7P 611227-24-8P 611227-25-9P
 611227-30-6P 611227-31-7P 611227-33-9P 611227-35-1P 611227-37-3P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(drug candidate; preparation of azaindoles as inhibitors of c-
jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT 155215-87-5, JNK 291756-39-3, JNK3

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitor; preparation of azaindoles as inhibitors of c-
jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT 113423-51-1P 183208-32-4P 183208-34-6P 611204-90-1P 611204-91-2P
 611204-92-3P 611226-88-1P 611226-89-2P 611226-90-5P 611226-92-7P
 611226-93-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(intermediate; preparation of azaindoles as inhibitors of c-
jun N-terminal kinases for
 treatment of neurodegenerative disorders)

IT 98-09-9, Phenylsulfonyl chloride 100-46-9, Benzylamine, reactions
 271-63-6, 7-Azaindole 768-35-4, 3-Fluorophenylboronic acid 18162-48-6,
 tert-Butyldimethylsilyl chloride

RL: RCT (Reactant); RACT (Reactant or reagent)
 (preparation of azaindoles as inhibitors of c-jun
N-terminal kinases for treatment of
 neurodegenerative disorders)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 13 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:173436 HCAPLUS

DOCUMENT NUMBER: 138:215352

TITLE: JNK inhibitors

INVENTOR(S): Nagaya, Hideaki; Kawano, Yasuhiko; Kamei, Takayuki

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 125 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003018020	A1	20030306	WO 2002-JP8465	20020822 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,				
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,				
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,				
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,				
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,				

TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
 PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
 NE, SN, TD, TG
 EP 1426050 A1 20040609 EP 2002-765344 20020822 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
 JP 2003137785 A2 20030514 JP 2002-242827 20020823 <--
 US 2004254189 A1 20041216 US 2004-487283 20040220 <--
 PRIORITY APPLN. INFO.: JP 2001-253602 A (20010823 <--
 WO 2002-JP8465 W 20020822 <--

OTHER SOURCE(S): MARPAT 138:215352

ED Entered STN: 07 Mar 2003

AB Inhibitors against **c-Jun N-terminal**

kinase, containing compds. represented by the general formula (A) or salts or prodrugs thereof: (I) wherein Ara and Arb are each an optionally substituted aromatic group, or Ara and Arb together with the carbon atom adjacent thereto may form a fused ring; Ba is an optionally substituted nitrogenous heterocycle; Xa and Ya are each independently (1) a free valency, (2) oxygen, (3) S(O)_p (wherein p is an integer of 0 to 2), (4) NR_d (wherein R_d is hydrogen or lower alkyl), or (5) a bivalent linear lower hydrocarbon group which may be substituted and/or interrupted by one to three heteroatoms; Aa is an optionally substituted five-membered ring; Ra and Rb are each independently (1) hydrogen, (2) halogeno, (3) optionally substituted hydrocarbyl, (4) acyl, or (5) optionally substituted hydroxyl; and Rc is (1) hydrogen, (2) hydroxyl which may be substituted with lower alkyl, or (3) carboxyl.

IC ICM A61K031-5025

ICS A61K045-00; C07D487-04; A61P001-00; A61P001-04; A61P001-18;
 A61P005-14; A61P007-00; A61P007-02; A61P009-00; A61P009-10;
 A61P011-00; A61P011-02; A61P011-06; A61P013-12; A61P015-00;
 A61P017-00; A61P017-02; A61P017-04; A61P017-06

CC 1-12 (Pharmacology)

Section cross-reference(s): 28, 63

IT Antitumor agents

Autoimmune disease

Glaucoma (disease)

Leukemia

Lupus erythematosus

Melanoma

(triazolopyridazine analogs as JNK gene inhibitors for treatment of related diseases)

IT 155215-87-5, **c-Jun N-terminal**

kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(triazolopyridazine analogs as JNK gene inhibitors for treatment of related diseases)

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 14 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:97416 HCAPLUS

DOCUMENT NUMBER: 138:137163

TITLE: Preparation of thienylmethylbenzamides as C-
JUN-N-terminal
kinase (JNK) inhibitors

INVENTOR(S): Rueckle, Thomas; Gotteland, Jean-Pierre; Thomas,
 Russell J.; Biamonte, Marco

PATENT ASSIGNEE(S): Applied Research Systems ARS Holding N.V., Neth.

SOURCE: Antilles
PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003010164	A1	20030206	WO 2002-EP7832	20020715 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2452259	AA	20030206	CA 2002-2452259	20020715 <--
EP 1409483	A1	20040421	EP 2002-767208	20020715 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
JP 2005504031	T2	20050210	JP 2003-515523	20020715 <--
US 2004248886	A1	20041209	US 2004-484744	20040630 <--
PRIORITY APPLN. INFO.:			EP 2001-116798	A 20010723 <--
			WO 2002-EP7832	W 20020715 <--

OTHER SOURCE(S): MARPAT 138:137163

ED Entered STN: 07 Feb 2003

AB Ar1C(:X)NR1(CH2)mAr2SO2NR2(CRaRb)n(CRa1Rb1)pNR3R4 [Ar1 = (substituted) aryl, heteroaryl; X = O, S; Ar2 = (substituted) arylene, heteroarylene; R1, R2 = H, alkyl; Ra, Ra1, Rb, Rb1 = H, alkyl; Ra and Ra1 or Rb1 together = atoms to form a (substituted) (unsatd.) 5-8 membered ring; R3 = H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, aralkyl, heteroaralkyl; R4 = H, CHR5R6; R5, R6 = H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, aralkyl, heteroaralkyl; R3 and Ra or Ra1 = atoms to form a 5-8 membered saturated ring; m = 1-5; n = 0-2; p = 1-10], were prepared

as efficient and selective inhibitors of JNK2 and -3 for the treatment of neuronal disorders, autoimmune diseases, cancer and cardiovascular diseases. Thus, 4-chloro-N-[5-[(3-hexylaminopropyl)methylsulfamoyl]thiophen-2-ylmethyl]benzamide [preparation from N-(3-aminopropyl)-N-methylcarbamic acid tert-Bu ester and 1-hexanal given] inhibited JNK3 with IC50 = 184 nM.

IC ICM C07D409-12

ICS C07D333-34; A61K031-38; A61P029-00

CC 27-8 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1

IT Nervous system, disease

(Huntington's chorea, treatment; preparation of thienylmethylbenzamides as C-JUN-N-terminal kinase inhibitors)

IT Ischemia

(cardiac, treatment; preparation of thienylmethylbenzamides as C-JUN-N-terminal kinase inhibitors)

IT Ischemia

(cerebral, treatment; preparation of thienylmethylbenzamides as C-JUN-N-terminal kinase inhibitors)

IT Intestine, neoplasm
(colorectal, treatment; preparation of thienylmethylbenzamides as C
-JUN-N-terminal kinase
inhibitors)

IT Kidney, disease
(failure, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Heart, disease
(infarction, treatment; preparation of thienylmethylbenzamides as C
-JUN-N-terminal kinase
inhibitors)

IT Intestine, disease
(inflammatory, treatment; preparation of thienylmethylbenzamides as
C-JUN-N-terminal kinase
inhibitors)

IT Reperfusion
Spinal cord, disease
(injury, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Brain, disease
Heart, disease
Kidney, disease
(ischemia, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Anti-Alzheimer's agents
Antiartherosclerotics
Antiarthritics
Antiasthmatics
Anticonvulsants
Antiparkinsonian agents
Antitumor agents
Cardiovascular agents
Human
(preparation of thienylmethylbenzamides as C-JUN-
N-terminal kinase inhibitors)

IT Ischemia
(renal, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Injury
(reperfusion, treatment; preparation of thienylmethylbenzamides as C
-JUN-N-terminal kinase
inhibitors)

IT Eye, disease
(retinopathy, treatment; preparation of thienylmethylbenzamides as
C-JUN-N-terminal kinase
inhibitors)

IT Shock (circulatory collapse)
(septic, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Injury
(spinal cord, treatment; preparation of thienylmethylbenzamides as C
-JUN-N-terminal kinase
inhibitors)

IT Brain, disease
(stroke, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Head, disease
(trauma, treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT Alzheimer's disease

Arteriosclerosis
Asthma
Cardiovascular system, disease
Epilepsy
Kidney, neoplasm
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Multiple sclerosis
Ovary, neoplasm
Pancreas, neoplasm
Parkinson's disease
Prostate gland, neoplasm
Rheumatoid arthritis
Testis, neoplasm
Transplant rejection

(treatment; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT 494775-13-2P 494775-14-3P 494775-15-4P 494775-16-5P 494775-17-6P
494775-18-7P 494775-19-8P 494775-20-1P 494775-21-2P 494775-22-3P
494775-23-4P 494775-24-5P 494775-25-6P 494775-26-7P 494775-27-8P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)

(claimed compound; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT 166964-34-7P 332082-86-7P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(intermediate; preparation of thienylmethylbenzamides as C-
JUN-N-terminal kinase inhibitors)

IT 289899-93-0, Kinase (phosphorylating), gene c-jun protein N-terminal, 2
291756-39-3, Kinase (phosphorylating), gene c-jun protein N-terminal, 3

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(preparation of thienylmethylbenzamides as C-**JUN-
N-terminal kinase inhibitors**)

IT 66-25-1, Hexanal 122-01-0, 4-Chlorobenzoyl chloride 426-59-5
455-19-6, 4-Trifluoromethylbenzaldehyde 26734-09-8, 3-Amino-2,2-
dimethylpropan-1-ol 27757-85-3, 2-Aminomethylthiophene 57260-73-8
57734-57-3, 2-Pyrrolidinemethanamine 75178-96-0 87120-72-7
142643-29-6 150349-36-3 184637-48-7, 3-Amino-1-N-tert-
butoxycarbonylpiperidine 205318-52-1 292606-35-0 317595-54-3

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of thienylmethylbenzamides as C-**JUN-
N-terminal kinase inhibitors**)

IT 494775-28-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)

(preparation of thienylmethylbenzamides as C-**JUN-
N-terminal kinase inhibitors**)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 15 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:927240 HCAPLUS

DOCUMENT NUMBER: 138:11405

TITLE: Store operated calcium influx inhibitors and methods
of use

INVENTOR(S): Parks, Thomas P.; Baker, Don R.

PATENT ASSIGNEE(S): Cellegy Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 127 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002096416	A1	20021205	WO 2002-US17112	20020531 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2445712	AA	20021205	CA 2002-2445712	20020531 <--
US 2003114353	A1	20030619	US 2002-160977	20020531 <--
US 6699886	B2	20040302		
EP 1390030	A1	20040225	EP 2002-734606	20020531 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004106537	A1	20040603	US 2003-670665	20030924 <--
US 6869961	B2	20050322		
PRIORITY APPLN. INFO.:			US 2001-295124P	P 20010531 <--
			US 2001-295129P	P 20010531 <--
			US 2002-160977	A1 20020531 <--
			WO 2002-US17112	W 20020531 <--

OTHER SOURCE(S): MARPAT 138:11405

ED Entered STN: 06 Dec 2002

AB The present invention provides store operated calcium influx inhibitor compds., pharmaceutical compns., and methods of use. The compds. are useful for treating an inflammatory disease or treating an inflammatory reaction. Preferably, compds., compns. and methods of this invention are used for treatment of inflammatory skin, pulmonary, musculoskeletal, and gastrointestinal diseases, as well as autoimmune disorders, transplantation treatment, and osteoporosis. The compds. of the present invention are preferably store-operated calcium influx (SOC) inhibitors which inhibit calcium uptake into non-excitabile cells in response to stimulus-mediated depletion of intracellular calcium storage pools. The SOC inhibitors preferably inhibit one or more of the following: calcium-dependent activation of nuclear factor of activated T cells, nuclear factor kB, the stress kinases c-Jun N-terminal kinase and exocytosis, resulting in the release or elaboration of inflammatory mediators. Examples of SOC inhibitors are statins in the δ -lactone form such as lovastatin, mevastatin and simvastatin, as well as the novel compound, I. Examples of enema, suppository, and controlled-release tablet formulations are given.

IC ICM A61K031-405

ICS A61K031-435

CC 1-7 (Pharmacology)

IT Asthma

Autoimmune disease

Cystic fibrosis

Emphysema

Inflammation

Keratosis

Lupus erythematosus

Multiple sclerosis

Osteoarthritis

Osteoporosis

Psoriasis

Rheumatoid arthritis

Skin, disease

(store operated calcium influx inhibitors for treating inflammatory and other diseases)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 16 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:814126 HCAPLUS

DOCUMENT NUMBER: 137:325327

TITLE: Preparation of thienyl-substituted pyrimidinyl, pyridinyl and triazinyl amines as inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases

INVENTOR(S): Cao, Jingrong; Green, Jeremy; Moon, Young-Choon; Wang, Jian; Ledebuer, Mark; Harrington, Edmund; Gao, Huai

PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: PCT Int. Appl., 137 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083667	A2	20021024	WO 2002-US11570	20020410 <--
WO 2002083667	A3	20030103		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2443487	AA	20021024	CA 2002-2443487	20020410 <--
US 2003096816	A1	20030522	US 2002-121035	20020410 <--
US 6642227	B2	20031104		
EP 1389206	A2	20040218	EP 2002-762067	20020410 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
JP 2004535381	T2	20041125	JP 2002-581422	20020410 <--
US 2004023963	A1	20040205	US 2003-437666	20030514 <--
PRIORITY APPLN. INFO.:			US 2001-283621P	P 20010413 <--
			US 2001-292974P	P 20010523 <--
			US 2001-329440P	P 20011015 <--
			US 2002-121035	A3 20020410 <--
			WO 2002-US11570	W 20020410 <--

OTHER SOURCE(S): MARPAT 137:325327

ED Entered STN: 25 Oct 2002

AB The present invention provides thienyl-substituted pyrimidinyl, pyridinyl

and triazinyl amines (shown as I, e.g. 2-methylsulfanyl-5-(2-phenylaminopyrimidin-4-yl)-4-(4-chlorophenyl)thiophene-3-carbonitrile): or a pharmaceutically acceptable derivative thereof, wherein A, B, Ra, R1, R2, R3 and R4 are as described in the specification. These compds. are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved in cell proliferation, cell death and response to extracellular stimuli; Lck and Src kinase. The invention also provides pharmaceutical compns. comprising the inhibitors of the invention and methods of using those compns. in the treatment and prevention of various disorders. Although the methods of preparation are not claimed, 42 example preps. of intermediates and I are included. Results of JNK, Src and Lck inhibition are tabulated for many I.

IC ICM C07D409-00

CC 27-8 (Heterocyclic Compounds (One Hetero Atom))

Section cross-reference(s): 1, 28

IT Angiogenesis

(neovascularization, eye; preparation of thienyl-substituted pyrimidinyl, pyridinyl and triazinyl amines as inhibitors of JNK and other protein kinases useful for treating various conditions)

IT Eye, disease

(neovascularization; preparation of thienyl-substituted pyrimidinyl, pyridinyl and triazinyl amines as inhibitors of JNK and other protein kinases useful for treating various conditions)

L638 ANSWER 17 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:615608 HCAPLUS

DOCUMENT NUMBER: 137:169523

TITLE: Preparation of azoles as JNK inhibitors

INVENTOR(S): Ohkawa, Shigenori; Naruo, Kenichi; Miwatashi, Seiji; Kimura, Hiroyuki; Kawamoto, Tomohiro

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: PCT Int. Appl., 246 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062792	A1	20020815	WO 2002-JP828	20020201 <--
WO 2002062792	C2	20021212		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
CA 2437248	AA	20020815	CA 2002-2437248	20020201 <--
JP 2002302445	A2	20021018	JP 2002-26187	20020201 <--
EP 1364949	A1	20031126	EP 2002-711276	20020201 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR			
US 2004063946	A1	20040401	US 2003-470751	20030730 <--
PRIORITY APPLN. INFO.:			JP 2001-27570	A 20010202 <--
			WO 2002-JP828	W 20020201 <--
OTHER SOURCE(S):	MARPAT 137:169523			

ED Entered STN: 16 Aug 2002
AB The title compds., e.g. I [R1 = F, OH, etc.; R2 = F, OH, etc.; R3 = H, F, etc.; R4 = (cycloalkyl-substituted) alkyl; R5 = alkyl, etc.; D = bond, alkylene; E = NH, etc.; HETCy = non-aromatic heterocyclic ring; further details on said heterocyclic ring are given], are prepared Compds. of this invention in vitro showed IC50 values of 0.03 μ M to 0.21 μ M against **JNK1 kinase**. In an in vitro test using THP-1 cells, compds. of this invention in vitro showed IC50 values of 0.002 μ M to 0.1 μ M against TNF- α production Formulations are given.
IC ICM C07D417-04
ICS C07D417-14; A61K031-4439; A61K031-4545; A61K031-506; A61P043-00; A61P001-18; A61P011-00; A61P017-00; A61P001-04; A61P007-00; A61P007-04; A61P021-04; A61P035-00; A61P035-02; A61P025-14; A61P009-10; A61P013-12; A61P027-06; A61P009-04
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 27, 63
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study) (MKK7, **JNK1**, and c-Jun gene cloning; preparation and effect of azoles with effect on TNF release and on JNK)
IT **Glaucoma (disease)**
(neovascularization-induced; preparation and effect of azoles with effect on TNF release and on JNK)
IT 155215-87-5, **c-Jun N-terminal kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of azoles as JNK and TNF inhibitors)
IT 289898-51-7, **JNK1 kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of azoles as JNK inhibitors)
IT 289898-51-7, **JNK1 kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (preparation of azoles as JNK inhibitors)
RN 289898-51-7 HCAPLUS
CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 18 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:332435 HCAPLUS

DOCUMENT NUMBER: 136:336850

TITLE: Drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis

INVENTOR(S): Wasylyk, Bohdan; Multon, Marie-Christine; Ayadi, Abdelkader; Zheng, Hong

PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.; Institut National de la Sante et de la Recherche Medicale (INSERM)

SOURCE: PCT Int. Appl., 99 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
-----	----	-----	-----	-----
WO 2002035235	A2	20020502	WO 2001-EP12987	20011023 <--

WO 2002035235 A3 20021128
 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
 EP 1202065 A1 20020502 EP 2000-402968 20001025 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL
 CA 2426292 AA 20020502 CA 2001-2426292 20011023 <--
 AU 2002019086 A5 20020506 AU 2002-19086 20011023 <--
 EP 1332372 A2 20030806 EP 2001-988863 20011023 <--
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
 JP 2004512051 T2 20040422 JP 2002-538167 20011023 <--
 US 2004053833 A1 20040318 US 2003-415181 20031003 <--
 PRIORITY APPLN. INFO.: EP 2000-402968 A 20001025 <--
 WO 2001-EP12987 W 20011023 <--

ED Entered STN: 03 May 2002

AB The present invention relates to the regulation of the activity of mouse and human NET (ERP/SAP-2) transcription factors and to compds. which modify or regulate NET protein activity. The invention further relates to methods of screening for agonists or antagonists of NET in order to identify new pro-angiogenic or anti-angiogenic compds. and to therapeutic uses of these compds. The invention also relates to transgenic animals bearing mutations in NET gene.

IC ICM G01N033-68

ICS A01K067-027; A61P009-00; A61P035-00

CC 6-3 (General Biochemistry)

Section cross-reference(s): 3, 13, 14

IT **Eye**

(choroid, diseases, treatment of; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

IT **Eye, disease**

(diabetic retinopathy, treatment of; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

IT **Eye, disease**

(intraocular, treatment of; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

IT **Eye, disease**

(retinopathy, premature, treatment of; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

IT 137632-07-6, ERK1 Kinase 137632-08-7, ERK2 Kinase 289898-51-7,

JNK1 Kinase 289899-93-0, JNK2 Kinase 291756-39-3,

JNK3 Kinase

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(NET phosphorylation by; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

IT 289898-51-7, JNK1 Kinase

RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(NET phosphorylation by; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

RN 289898-51-7 HCAPLUS
CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L638 ANSWER 19 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:371640 HCAPLUS

DOCUMENT NUMBER: 137:106731

TITLE: ACK family tyrosine kinase activity is a component of
Dcdc42 signaling during dorsal closure in *Drosophila*
melanogaster

AUTHOR(S): Sem, Kai Ping; Zahedi, Baharak; Tan, Ivan; Deak,
Maria; Lim, Louis; Harden, Nicholas

CORPORATE SOURCE: Department of Molecular Biology and Biochemistry,
Simon Fraser University, Burnaby, BC, V5A 1S6, Can.

SOURCE: Molecular and Cellular Biology (2002),
22(11), 3685-3697

CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 May 2002

AB We have characterized *D. melanogaster* ACK (DACK), 1 of 2 members of the
ACK family of nonreceptor tyrosine kinases in *Drosophila*. The ACKs are
likely effectors for the small GTPase Cdc42, but signaling by these
proteins remains poorly defined. ACK family tyrosine kinase activity
functions downstream of *Drosophila* Cdc42 during dorsal closure of the
embryo, as overexpression of DACK can rescue the dorsal closure defects
caused by dominant-neg. Dcdc42. Similar to known participants in dorsal
closure, DACK is enriched in the leading edge cells of the advancing
epidermis, but it does not signal through activation of the Jun
amino-terminal kinase cascade operating in these cells. Transcription of
DACK is responsive to changes in Dcdc42 signaling specifically at the
leading edge and in the amnioserosa, 2 tissues involved in dorsal closure.
Unlike other members of the ACK family, DACK does not contain a conserved
Cdc42-binding motif, and transcriptional regulation may be 1 route by
which Dcdc42 can affect DACK function. Expression of wild-type and
kinase-dead DACK transgenes in embryos, and in the developing wing and
eye, reveals that ACK family tyrosine kinase activity is involved
in a range of developmental events similar to that of Dcdc42.

CC 12-3 (Nonmammalian Biochemistry)

Section cross-reference(s): 3, 7

IT Development, nonmammalian postembryonic

Drosophila melanogaster

Embryo, animal

Eye

Genetic mapping

Protein sequences

Signal transduction, biological

Wing, anatomical

cDNA sequences

(ACK tyrosine kinase sequence and role in cdc42 signaling during dorsal
closure in *Drosophila* embryos)

IT 9059-32-9, GTPase 155215-87-5, **c-Jun N-**
terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(ACK tyrosine kinase sequence and role in cdc42 signaling during dorsal
closure in *Drosophila* embryos)

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 20 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:540671 HCAPLUS

DOCUMENT NUMBER: 137:260255

TITLE: Eiger, a TNF superfamily ligand that triggers the Drosophila JNK pathway

AUTHOR(S): Igaki, Tatsushi; Kanda, Hiroshi; Yamamoto-Goto, Yuki; Kanuka, Hirotaka; Kuranaga, Erina; Aigaki, Toshiro; Miura, Masayuki

CORPORATE SOURCE: Laboratory for Cell Recovery Mechanisms, Brain Science Institute, RIKEN, Saitama, 351-0198, Japan

SOURCE: EMBO Journal (2002), 21(12), 3009-3018

CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 21 Jul 2002

AB Drosophila provides a powerful genetic model for studying the in vivo regulation of cell death. In our large-scale gain-of-function screen, we identified Eiger, the 1st invertebrate tumor necrosis factor (TNF) superfamily ligand that can induce cell death. Eiger is a type II transmembrane protein with a C-terminal TNF homol. domain. It is predominantly expressed in the nervous system. Genetic evidence shows that Eiger induces cell death by activating the Drosophila JNK pathway. Although this cell death process is blocked by Drosophila inhibitor-of-apoptosis protein 1 (DIAP1), it does not require caspase activity. Genetically Eiger is a physiol. ligand for the Drosophila JNK pathway. Our findings demonstrate that Eiger can initiate cell death through an IAP-sensitive cell death pathway via JNK signaling.

CC 12-3 (Nonmammalian Biochemistry)

Section cross-reference(s): 3, 6

IT Apoptosis

Brain

Development, nonmammalian postembryonic

Drosophila melanogaster

Eye

Protein sequences

Signal transduction, biological

Species differences

Wing, anatomical

cDNA sequences

(Eiger protein sequence and role in triggering Drosophila JNK pathway)

IT 186322-81-6, Caspase 289898-51-7, c-Jun

N-terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(Eiger protein sequence and role in triggering Drosophila JNK pathway)

IT 289898-51-7, c-Jun N-

terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(Eiger protein sequence and role in triggering Drosophila JNK pathway)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 21 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:251475 HCAPLUS
DOCUMENT NUMBER: 137:45236
TITLE: Reactive oxygen species accelerate production of
vascular endothelial growth factor by advanced
glycation end products in RAW264.7 mouse macrophages
AUTHOR(S): Urata, Yoshishige; Yamaguchi, Michiko; Higashiyama,
Yasuhito; Ihara, Yoshito; Goto, Shinji; Kuwano,
Michihiko; Horiuchi, Seikoh; Sumikawa, Koji; Kondo,
Takahito
CORPORATE SOURCE: Atomic Bomb Disease Institute, Department of
Biochemistry and Molecular Biology in Disease,
Nagasaki University School of Medicine, Nagasaki,
Japan
SOURCE: Free Radical Biology & Medicine (2002),
32(8), 688-701
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 04 Apr 2002
AB Advanced glycation end products (AGEs) are believed to play an important
role in the development of angiopathy in diabetes mellitus. Previous
reports suggested a correlation between accumulation of AGEs and production of
vascular endothelial growth factor (VEGF) in human diabetic retina.
However, the mechanisms involved were not revealed. In this study, we
investigated the transcriptional regulation of the expression of vascular
endothelial growth factor (VEGF) by AGEs, and possible involvement of
reactive oxygen species (ROS) in the induction. We employed an AGE of
bovine serum albumin (BSA) prepared by an incubation of BSA with D-glucose
for 40 wk and N(epsilon)-(carboxymethyl)lysine (CML), a major AGE. The
expression of VEGF was induced by CML-BSA in RAW264.7 mouse
macrophage-like cells. CML-BSA stimulated the DNA-binding activity of
activator protein-1 (AP-1). Promoter assay showed that the induction of
VEGF was dependent on AP-1. The activity of Ras/Raf-1/MEK/ERK1/2 was
involved in the CML-BSA-stimulated signaling pathways to activate the AP-1
transcription with a peak at 1 h. AGE-BSA also induced VEGF mediated by
AP-1, however, there was a difference of effect between AGE-BSA and
CML-BSA in the activation of AP-1. AGE-BSA-stimulated AP-1 activity
showed a peak at 5 h, which paralleled the formation of ROS. Reduction of
AGE-BSA with NaBH4 or addition of vitamin E attenuated the AGE-BSA-stimulated
signaling pathways leading to the same pattern as for CML-BSA-stimulated
signals. These results suggest an important role for AGEs in stimulation
of the development of angiogenesis observed in diabetic complications, and
that ROS accelerates the AGE-stimulated VEGF expression.
CC 14-8 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
IT **Eye, disease**
(diabetic retinopathy; reactive oxygen species
accelerate advanced glycation end products induced expression of VEGF
mRNA mediated by AP-1 in macrophages in diabetic angiopathy)
IT 1406-18-4, Vitamin E 137632-07-6, ERK-1 kinase 137632-08-7, ERK-2
kinase 139691-76-2, Raf-1 kinase 155215-87-5, c-Jun
N-terminal kinase 165245-96-5, p38 MAP
Kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reactive oxygen species accelerate advanced glycation end products
induced expression of VEGF mRNA mediated by AP-1 in macrophages in
diabetic angiopathy)
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 22 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:203343 HCAPLUS

DOCUMENT NUMBER: 136:365821

TITLE: Selective induction of mitogen-activated protein kinases in human lens epithelial cells by ultraviolet radiation

AUTHOR(S): Bomser, Joshua A.

CORPORATE SOURCE: Department of Food Science and Technology, The Ohio State University, Columbus, OH, 43210, USA

SOURCE: Journal of Biochemical and Molecular Toxicology (2002), 16(1), 33-40

CODEN: JBMTFQ; ISSN: 1095-6670

PUBLISHER: John Wiley & Sons, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 19 Mar 2002

AB The present study investigates the effects of UV radiation (UVR) on mitogen-activated protein kinase (MAPK) activity in human lens epithelial (HLE) cells. Irradiation of HLE cells with UV B and UV C radiation activates the stress-response MAPK proteins, p38 and c-Jun NH2-terminal kinase (JNK), in a dose- and time-dependent manner, while the extracellular-regulated signal kinase (ERK) 44/42 cascade was not altered by UVR exposure. UV A radiation failed to elicit a MAPK response. UVR-induced MAPK activation does not require protein kinase C or phosphatidylinositol 3-kinase activity, suggesting that this is not a receptor-mediated event. Inhibition of ribosomal translation completely abolished UVR-induced MAPK activation, while treatment with the antioxidant, N-acetyl cysteine, and mild heat shock had no effect on this activation. These data demonstrate for the first time the selective activation of MAPK cascades in a lens epithelial cell line.

CC 8-7 (Radiation Biochemistry)

ST eye lens mitogen activated protein kinase UV radiation

IT Eye

(lens, epithelium; induction of mitogen-activated protein kinases in human lens epithelial cells by UV radiation)

IT 115926-52-8, Phosphatidylinositol 3-kinase 137632-07-6, p44 MAP kinase 137632-08-7, p42 MAP kinase 141436-78-4, Protein kinase C 142243-02-5, Mitogen-activated protein kinase 155215-87-5, c-Jun kinase 192230-91-4, JNK/p38 kinase 289898-51-7, p46JNK kinase 289899-93-0, p54JNK kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (induction of mitogen-activated protein kinases in human lens epithelial cells by UV radiation)

IT 289898-51-7, p46JNK kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (induction of mitogen-activated protein kinases in human lens epithelial cells by UV radiation)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 23 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:472481 HCAPLUS

DOCUMENT NUMBER: 135:71275

TITLE: Use of phenethylamine derivatives such as

2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium
chloride as anti-inflammatory agents

INVENTOR(S): De Bosscher, Karolien; Vanden Berghe, Wim; Haegeman, Guy

PATENT ASSIGNEE(S): Vlaams Interuniversitair Instituut Voor Biotechnologie
Vzw, Belg.

SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045693	A1	20010628	WO 2000-EP13347	20001221 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2395119	AA	20010621	CA 2000-2395119	20001221 <--
AU 2001021731	A5	20010703	AU 2001-21731	20001221 <--
EP 1239850	A1	20020918	EP 2000-985264	20001221 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003055030	A1	20030320	US 2002-177987	20020621 <--
PRIORITY APPLN. INFO.:			EP 1999-204433	A 19991221 <--
			WO 2000-EP13347	W 20001221 <--

OTHER SOURCE(S): MARPAT 135:71275

ED Entered STN: 29 Jun 2001

AB The invention relates to the use of phenethylamine derivs., more specifically to the use of 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride, in the treatment of inflammatory diseases. Part of the invention is also a composition, preferably a pharmaceutical composition,

comprising as active ingredient at least 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride together with (pharmaceutically) acceptable excipients.

IC ICM A61K031-137

ICS A61P011-06; A61P017-00; A61P017-06; A61P019-02

CC 1-7 (Pharmacology)

IT Blood vessel, disease

Eye, disease

Infection

Multiple sclerosis

Neoplasm

(inflammation associated with; phenethylamine derivs. to prevent and/or treat inflammatory diseases and inflammation associated disorders)

IT 137632-07-6, p44 ERK Kinase 137632-08-7, p42 ERK Kinase 165245-96-5, p38 MAP Kinase 289898-51-7, p46JNK kinase 289899-93-0, p54JNK kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(phenethylamine derivs. to prevent and/or treat inflammatory diseases

and inflammation associated disorders)
 IT 289898-51-7, p46JNK kinase
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
 (Biological study); PROC (Process)
 (phenethylamine derivs. to prevent and/or treat inflammatory diseases
 and inflammation associated disorders)
 RN 289898-51-7 HCAPLUS
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 24 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:338762 HCAPLUS

DOCUMENT NUMBER: 134:362292

TITLE: Methods of determining individual hypersensitivity to
 a pharmaceutical agent from gene expression profile

INVENTOR(S): Farr, Spencer

PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA

SOURCE: PCT Int. Appl., 222 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103 <--
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105 <--
 US 2000-196571P P 20000411 <--

ED Entered STN: 11 May 2001

AB The invention discloses methods, gene databases, gene arrays, protein
 arrays, and devices that may be used to determine the hypersensitivity of
 individuals to a given agent, such as drug or other chemical, in order to
 prevent toxic side effects. In one embodiment, methods of identifying
 hypersensitivity in a subject by obtaining a gene expression profile of
 multiple genes associated with hypersensitivity of the subject suspected to
 be hypersensitive, and identifying in the gene expression profile of the
 subject a pattern of gene expression of the genes associated with
 hypersensitivity are disclosed. The gene expression profile of the
 subject may be compared with the gene expression profile of a normal
 individual and a hypersensitive individual. The gene expression profile
 of the subject that is obtained may comprise a profile of levels of mRNA
 or cDNA. The gene expression profile may be obtained by using an array of
 nucleic acid probes for the plurality of genes associated with
 hypersensitivity. The expression of the genes predetd. to be associated with
 hypersensitivity is directly related to prevention or repair of toxic

damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

- IC ICM C12Q001-68
- ICS G01N033-50
- CC 3-4 (Biochemical Genetics)
- Section cross-reference(s): 1, 6, 7, 13, 15
- IT Gene, animal
- RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
- (JNK1; methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)
- IT Aging, animal
- Allergy
- Apparatus
- Astrocyte
- Bone
- Brain
- Bronchodilators
- Computer program
- DNA microarray technology
- Digestive tract
- Dione
- Drugs
- Eye
- Fibroblast
- Gallbladder
- Hepatitis
- Hyperplasia
- Hypertension
- Hypotension
- Immunosuppression
- Inflammation
- Intestine
- Jaundice
- Kidney
- Leukemia
- Leukocyte
- Liver
- Macrophage
- Mast cell
- Muscle
- Mutagenesis
- Necrosis
- Nucleic acid hybridization
- Oligodendrocyte
- Ovary
- Pancreas
- Plantago psyllium
- Podophyllum (plant)
- Sex
- Skin
- Spleen
- Statistical analysis
- Stomach
- Testis
- Thyroid gland
- (methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT **Eye, disease**

(retinopathy; methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile)

IT 107-97-1, Sarcosin 447-41-6, Nylidrin 8056-51-7 9000-86-6, Alanine aminotransferase 9000-97-9 9001-05-2, Catalase 9001-40-5, Glucose-6-phosphate dehydrogenase 9001-48-3, Glutathione reductase 9001-50-7, Glyceraldehyde 3-phosphate dehydrogenase 9001-62-1, Hepatic lipase 9001-84-7, Phospholipase A2 9002-03-3, Dihydrofolate reductase 9002-06-6, Thymidine kinase 9002-12-4, Urate oxidase 9002-67-9, Luteinizing hormone 9003-99-0, Myeloperoxidase 9012-25-3, Catechol-O-methyltransferase 9012-38-8, PAPS synthetase 9012-39-9 9012-52-6, S-Adenosylmethionine synthetase 9013-08-5, Phosphoenolpyruvate carboxykinase 9013-18-7, Fatty acyl-CoA synthetase 9013-38-1, Dopamine β -hydroxylase 9013-66-5, Glutathione peroxidase 9013-79-0, Neuropathy target esterase 9014-55-5, Tyrosine aminotransferase 9015-71-8, Corticotropin releasing hormone 9015-81-0, 17- β Hydroxysteroid dehydrogenase 9016-12-0, Hypoxanthine-guanine phosphoribosyltransferase 9023-44-3, Tryptophanyl-tRNA synthetase 9023-62-5, Glutathione synthetase 9023-64-7, γ -Glutamylcysteinyl synthetase 9023-70-5, Glutamine synthetase 9024-60-6, Ornithine decarboxylase 9024-61-7, Histidine decarboxylase 9025-32-5, Prolidase 9026-00-0, Cholesterol esterase 9026-09-9, Phenol sulfotransferase 9026-43-1, Serine kinase 9026-51-1, Nucleoside diphosphate kinase 9027-13-8, Enoyl-CoA hydratase 9027-65-0, Acyl-CoA dehydrogenase 9028-06-2 9028-31-3, Aldose reductase 9028-35-7, HMG CoA reductase 9028-41-5, Hydroxyacyl-Coenzyme A dehydrogenase 9028-86-8, Aldehyde dehydrogenase 9029-73-6, Phenyl alanine hydroxylase 9029-80-5, Histamine N-methyltransferase 9029-97-4, 3-Ketoacyl-CoA thiolase 9031-37-2, Ceruloplasmin 9031-54-3, Sphingomyelinase 9031-61-2, Thymidylate synthase 9031-72-5, Alcohol dehydrogenase 9032-20-6, DT-Diaphorase 9032-76-2 9035-58-9, Blood-coagulation factor III 9036-22-0, Tyrosine hydroxylase 9037-21-2, Tryptophan hydroxylase 9037-62-1, Glycyl tRNA synthetase 9039-06-9, NADPH cytochrome P450 reductase 9040-57-7, Ribonucleotide reductase 9041-92-3 9045-77-6, Fatty acid synthase 9046-27-9, γ -Glutamyl transpeptidase 9048-63-9, Epoxide hydrolase 9055-67-8, Poly(ADP-ribose)polymerase 9059-25-0, Lysyl oxidase 9068-41-1, Carnitine palmitoyltransferase 9074-02-6, Malic enzyme 9074-10-6, Biliverdin reductase 9074-19-5, Hydratase 9074-87-7, γ -Glutamyl hydrolase 9081-36-1, 25-Hydroxyvitamin D3 1-hydroxylase 11096-26-7, Erythropoietin 37205-63-3, ATP synthase 37237-44-8, Glucosylceramide synthase 37289-06-8, Acid ceramidase 37292-81-2, Cytochrome p 450 11A1 37318-49-3, Protein disulfide isomerase 39391-18-9, Prostaglandin H synthase 56093-23-3, α -1,2-Fucosyl transferase 56645-49-9, Cathepsin G 59536-73-1, Phosphomannomutase 59536-74-2, Very long-chain acyl-CoA dehydrogenase 60267-61-0, Ubiquitin 60616-82-2, Cathepsin L 61116-22-1, Fatty acyl-CoA oxidase 62229-50-9, Epidermal growth factor 67339-09-7, Thiopurine methyltransferase 67763-96-6, Insulin-like growth factor 1 67763-97-7, Insulin-like growth factor II 77271-19-3, 6-O-Methylguanine-DNA methyltransferase 77847-96-2, Prostacyclin-stimulating factor 79747-53-8, Protein tyrosine phosphatase 79955-99-0, Stromelysin-1 80146-85-6, Tissue Transglutaminase 80295-41-6, Complement component C3 81627-83-0, Colony stimulating factor -1 82391-43-3, 12-Lipoxygenase 83268-44-4 83869-56-1, Granulocyte-macrophage colony-stimulating factor 85637-73-6, Atrial natriuretic factor 87397-91-9, Thymosin β 10 88943-21-9, Proteinase α 1-inhibitor III 89964-14-7, Prothymosin, alpha 90698-26-3, Ribosomal protein S6 kinase 96024-44-1, Granulin 105238-46-8, Macropain 106096-92-8, Fibroblast growth factor, acidic 106956-32-5, Oncostatin M 112130-98-0, Procathepsin L 114949-22-3,

Activin (protein) 117698-12-1, Paraoxonase 119418-04-1, Galanin 122191-40-6, Caspase-1 123626-67-5, Endothelin-1 125978-95-2, Nitric oxide synthase 127464-60-2, Vascular endothelial growth factor 137632-07-6, Extracellular-signal-regulated kinase 1 138238-81-0, Endothelin converting enzyme-1 140208-24-8, Tissue inhibitor of metalloproteinase-1 141176-92-3 141349-86-2, Cyclin dependent kinase 2 141436-78-4, Protein kinase C 142243-03-6, Plasminogen activator inhibitor 2 142805-56-9, DNA topoisomerase II 142805-58-1, MAP kinase kinase 143180-75-0, DNA topoisomerase I 143375-65-9, Cyclin dependent kinase 1 145809-21-8, Tissue inhibitor of metalloproteinase-3 146480-35-5, Matrix metalloproteinase-2 147014-97-9, Cyclin dependent kinase 4 148348-15-6, Fibroblast growth factor 7 149316-81-4, Branched chain acyl-CoA oxidase 149371-05-1, Kinase (phosphorylating), gene c-abl protein 149885-78-9, Hepatocyte growth factor activator 154907-65-0, Checkpoint kinase 155807-64-0, FEN-1 Endonuclease 165245-96-5, p38 Mitogen-activated protein kinase 169592-56-7, CPP32 proteinase 179241-70-4, Protein kinase ZPK 179241-78-2, Caspase 8 182372-14-1, Caspase 2 182372-15-2, Caspase 6 182762-08-9, Caspase 4 189258-14-8, Caspase 7 192465-11-5, Caspase 5 193363-12-1, Vascular endothelial growth factor D 194554-71-7, Tissue factor pathway inhibitor 205944-50-9, Osteoprotegerin 220983-94-8, Sorbitol dehydrogenase 289898-51-7, **JNK1 protein kinase** 303752-61-6, DNA dependent protein kinase 329736-03-0, Cytochrome p450 3A4 329764-85-4, Cytochrome p450 1A1 329900-75-6, Cyclooxygenase 2 329978-01-0, Cytochrome p450 2C9 330196-64-0, Cytochrome p450 1A2 330196-93-5, Cytochrome p450 2E1 330207-10-8, Cytochrome p450 2B1 330589-90-7, Cytochrome p450 2C19 330596-22-0, Cytochrome p450 1B1 330597-62-1, Cytochrome p450 2D6 330975-22-9, Macrostatin 331462-97-6, Cytochrome p450 2B2 331462-98-7, Cytochrome p450 3A1 331823-00-8, Cytochrome p450 2C11 331823-12-2, Cytochrome p450 2C12 331823-27-9, Cytochrome p450 2A1 331827-06-6, Cytochrome p450 2A6 332847-52-6, Cytochrome p450 4A 336884-26-5, Cytochrome p450 2B10 338964-08-2, P 450 17A 338969-62-3, P 450 2A3 338969-69-0, P 450 2F2 338969-71-4, P 450 4A1

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(methods of determining individual hypersensitivity to a pharmaceutical

agent

from gene expression profile)

IT 289898-51-7, **JNK1 protein kinase**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(methods of determining individual hypersensitivity to a pharmaceutical

agent

from gene expression profile)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L638 ANSWER 25 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:125925 HCAPLUS

DOCUMENT NUMBER: 136:151160

TITLE: Preparation of N-thienylsulfonylthiazolecarbohydrazide
s and analogs as c-Jun N
-terminal kinase inhibitors

INVENTOR(S): Arkinstall, Stephen; Halazy, Serge; Church, Dennis;
Camps, Montserrat; Rueckle, Thomas; Gotteland,
Jean-Pierre; Biamonte, Marco

PATENT ASSIGNEE(S): Applied Research Systems ARS Holding N.V., Neth.
Antilles
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001023382	A1	20010405	WO 2000-IB1381	20000928 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1088822	A1	20010404	EP 1999-810870	19990928 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2385001	AA	20010405	CA 2000-2385001	20000928 <--
EP 1216245	A1	20020626	EP 2000-962745	20000928 <--
EP 1216245	B1	20040526		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003510323	T2	20030318	JP 2001-526534	20000928 <--
AT 267826	E	20040615	AT 2000-962745	20000928 <--
AU 777293	B2	20041007	AU 2000-74386	20000928 <--
PRIORITY APPLN. INFO.:			EP 1999-810870	A 19990928 <--
			WO 2000-IB1381	W 20000928 <--

OTHER SOURCE(S): MARPAT 136:151160

ED Entered STN: 19 Feb 2002

AB RC(:X1)NR1(CH2)nZSO2NR2NR3C(:X2)R4 [I; R = (un)substituted (hetero)aryl; R1, R2, and R3 = H or alkyl; or RR1 and/or R2R3 = atoms to complete a ring; R4 = (un)substituted alkyl or heterocyclyl; X1 and X2 = O or S; Z = (un)substituted (hetero)arylene; n = 0-5] were prepared as c-

Jun N-terminal kinase (JNK)

inhibitors, especially JNK2 or JNK3 inhibitors. Thus, 2-thiophenemethanamine was amidated by 4-ClC6H4COCl (98%) and the chlorosulfonated product (63%) amidated by 2-[4-(1,3-dithiolan-2-yl)phenyl]thiazole-4-carbohydrazide to give title compound II (80%). The latter exhibited selective inhibitory effect for JNK2 and JNK3 compared with p38 kinase and ERK2 protein kinase with IC50 values of 0.21 μ M, 0.37 μ M, >30 μ M, and >30 μ M, resp. Thus, I are useful for the treatment of neuronal disorders, autoimmune diseases, cancer, and cardiovascular disease.

IC ICM C07D417-14

ICS C07D417-12; C07D409-14; C07D409-12; C07D213-74; A61K031-4436; A61K031-4439; A61K031-44

CC 28-7 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

IT **Eye, disease**

(retinopathy, treatment; preparation of N-thienylsulfonylthiazolecarbohydrazides and analogs as JNK2 and JNK3 inhibitors for treatment of neuronal disorders, autoimmune diseases, cancer, and cardiovascular disease)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 26 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:471524 HCAPLUS

DOCUMENT NUMBER: 135:208892

TITLE: Kinesin molecular motors: transport pathways, receptors, and human disease

AUTHOR(S): Goldstein, Lawrence S. B.

CORPORATE SOURCE: Howard Hughes Medical Institute, Department of Cellular and Molecular Medicine, University of California at San Diego School of Medicine, La Jolla, CA, 92093-0683, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(13), 6999-7003

CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 29 Jun 2001

AB A review, with 66 refs.,. Kinesin mol. motor proteins are responsible for many of the major microtubule-dependent transport pathways in neuronal and non-neuronal cells. Elucidating the transport pathways mediated by kinesins, the identity of the cargoes moved, and the nature of the proteins that link kinesin motors to cargoes are areas of intense investigation. Kinesin-II recently was found to be required for transport in motile and non-motile cilia and flagella where it is essential for proper left-right determination in mammalian development, sensory function in ciliated neurons, and opsin transport and viability in photoreceptors. Thus, these pathways and proteins may be prominent contributors to several human diseases including ciliary dyskinesias, situs inversus, and retinitis pigmentosa. Kinesin-I is needed to move many different types of cargoes in neuronal axons. Two candidates for receptor proteins that attach kinesin-I to vesicular cargoes were recently found. One candidate, sunday driver, is proposed to both link kinesin-I to an unknown vesicular cargo and to bind and organize the mitogen-activated protein kinase components of a **c-Jun N-terminal kinase** signaling module. A second candidate, amyloid precursor protein, is proposed to link kinesin-I to a different, also unknown, class of axonal vesicles. The finding of a possible functional interaction between kinesin-I and amyloid precursor protein may implicate kinesin-I based transport in the development of Alzheimer's disease.

CC 14-0 (Mammalian Pathological Biochemistry)

IT **Eye, disease**

(retinitis pigmentosa; kinesin mol. motors: transport pathways, receptors, and human disease)

REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 27 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:881129 HCAPLUS

DOCUMENT NUMBER: 134:42135

TITLE: Preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**.

INVENTOR(S): Salituro, Francesco; Bemis, Guy; Green, Jeremy; Fejzo, Jasna; Xie, Xiaoling

PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA

SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075118	A1	20001214	WO 2000-US15248	20000602 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003100549	A1	20030529	US 2001-8277	20011203 <--
PRIORITY APPLN. INFO.:			US 1999-137523P	P 19990603 <--
			WO 2000-US15248	A1 20000602 <--

OTHER SOURCE(S): MARPAT 134:42135

ED Entered STN: 15 Dec 2000

AB Title compds. [I; Y = O, NH, NR, S, SO, SO₂; X = O, NH, NR; R₁, R₂ = H, (substituted) alkyl, alkenyl, (aromatic) (bicyclic) carbocyclyl, heterocyclyl; R = alkyl, alkenyl, (aromatic) (bicyclic) carbocyclyl, heterocyclyl], were prepared as inhibitors of **c-JUN N-terminal kinases**. Thus, I (R₁Y, R₂X = PhNH) inhibited JNK3 with IC₅₀ <1 µM.

IC ICM C07D239-54

ICS C07D401-12; A61K031-505; C07D401-12; C07D239-00; C07D213-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

IT Intestine, disease

(Crohn's, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Nervous system

(Huntington's chorea, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Sarcoma

(Kaposi's, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Respiratory distress syndrome

(adult, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Nervous system

(amyotrophic lateral sclerosis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Dermatitis

(atopic, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Heart, disease

(attack, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Stomach, disease
(autoimmune gastritis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Nervous system
(degeneration, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Kidney, disease
(glomerulonephritis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Transplant and Transplantation
(graft-vs.-host reaction, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Anemia (disease)
(hemolytic, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Heart, disease
(hypertrophy, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Intestine, disease
(inflammatory, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Reperfusion
(injury, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Brain, disease
(ischemia, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Antitumor agents
(leukemia; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Angiogenesis
(neovascularization, treatment or **ocular** neovascularization; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Agranulocytosis
(neutropenia, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Pancreas, disease
(pancreatitis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Allergy inhibitors
Anti-Alzheimer's agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Antidiabetic agents
Antiparkinsonian agents
Antitumor agents
Bone, disease

Platelet aggregation inhibitors
 (preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Connective tissue
 (scleroderma, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Brain, disease
 (stroke, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Osteoporosis
 (therapeutic agents; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Platelet (blood)
 (thrombocytopenia, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Thyroid gland, disease
 (thyroiditis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Cytokines
 RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
 (treatment of disorders associated with proinflammatory cytokines; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Angiogenesis
 Cell proliferation
 (treatment of disorders; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Immunity
 (treatment of pathol. immune response; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Hyperplasia
 (treatment of vascular hyperplasia; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Autoimmune disease
 Graves' disease
 Hepatitis
 Hypoxia, animal
 Infection
 Lupus erythematosus
 Melanoma
 Multiple myeloma
 Multiple sclerosis
 Myasthenia gravis
 Psoriasis
 (treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT Intestine, disease
 (ulcerative colitis, treatment; preparation of pyrimidinediones as inhibitors of **c-JUN N-terminal kinases**)

IT 289898-51-7, c-JUN N-terminal kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 264884-33-5 312752-09-3 312752-10-6 312752-12-8 312752-13-9
312752-15-1 312752-17-3 312752-19-5 312752-21-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 62-53-3, Aniline, reactions 108-59-8, Dimethyl malonate 10191-60-3, Dimethyl N-cyanodithioiminocarbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 136411-38-6P 312752-23-1P 312752-24-2P 312752-25-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

IT 289898-51-7, c-JUN N-terminal kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(inhibitors; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

RN 289898-51-7 HCAPLUS
CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 28 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:405243 HCAPLUS

DOCUMENT NUMBER: 133:147642

TITLE: The roles of the Drosophila JAK/STAT pathway

AUTHOR(S): Zeidler, Martin P.; Bach, Erika A.; Perrimon, Norbert

CORPORATE SOURCE: Department of Genetics, Howard Hughes Medical Institute, Harvard Medical School, Boston, MA, 02115, USA

SOURCE: Oncogene (2000), 19(21), 2598-2606

CODEN: ONCNES; ISSN: 0950-9232

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 20 Jun 2000

AB A review, with 38 refs. The JAK/STAT signal transduction pathway has been conserved throughout evolution such that true structural and functional homologs of components originally identified in vertebrate systems are also present in the model genetic system Drosophila melanogaster. In addition to roles during larval hematopoiesis reminiscent of the requirement for this pathway in mammalian systems, the JAK/STAT pathway in Drosophila is also involved in a number of other developmental events. Recent data has demonstrated further roles for the JAK/STAT pathway in the establishment of sexual identity via the early embryonic expression of Sex lethal, the

segmentation of the embryo via the control of pair rule genes including even skipped and the establishment of polarity within the adult compound eye via a mechanism that includes the 4 jointed gene. Use of the powerful genetics in the model organism *Drosophila* may identify new components of the JAK/STAT pathway, define new roles for this pathway, and provide insights into the function of this signal transduction system. Here we review the roles of STAT and its associated signaling pathway during both embryonic and adult stages of *Drosophila* development and discuss future prospects for the identification and characterization of novel pathway components and targets.

CC 12-0 (Nonmammalian Biochemistry)

IT 155215-87-5, **c-Jun N-terminal kinase**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(roles of *Drosophila* JAK/STAT pathway)

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 29 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:834930 HCAPLUS

DOCUMENT NUMBER: 134:129049

TITLE: Gene expression in the brain across the sleep-waking cycle

AUTHOR(S): Cirelli, C.; Tononi, G.

CORPORATE SOURCE: The Neurosciences Institute, San Diego, CA, 92121, USA

SOURCE: Brain Research (2000), 885(2), 303-321

CODEN: BRREAP; ISSN: 0006-8993

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 29 Nov 2000

AB Sleep and waking differ significantly in terms of behavior, metabolism, and neuronal activity. Recent evidence indicates that sleep and waking also differ with respect to the expression of certain genes. To systematically investigate such changes, we used mRNA differential display and cDNA microarrays to screen .apprx.10000 transcripts expressed in the cerebral cortex of rats after 8 h of sleep, spontaneous waking, or sleep deprivation. We found that 44 genes had higher mRNA levels after waking and/or sleep deprivation relative to sleep, while 10 were upregulated after sleep. Known genes that were upregulated in waking and sleep deprivation can be grouped into the following categories: immediate early genes/transcription factors (Arc, CHOP, IER5, NGFI-A, NGFI-B, N-Ras, Stat3), genes related to energy metabolism (glucose type I transporter Glut1, Vgf), growth factors/adhesion mol. (BDNF, TrkB, F3 adhesion mol.), chaperones/heat shock proteins (BiP, ERP72, GRP75, HSP60, HSP70), vesicle- and synapse-related genes (chromogranin C, synaptotagmin IV), neurotransmitter/hormone receptors (adrenergic receptor α 1A and β 2, GABAA receptor β 3, glutamate NMDA receptor 2A, glutamate AMPA receptor GluR2 and GluR3, nicotinic acetylcholine receptor β 2, thyroid hormone receptor TR β), neurotransmitter transporters (glutamate/aspartate transporter GLAST, Na⁺/Cl⁻ transporter NTT4/Rxt1), enzymes (aryl sulfotransferase, c-jun N-terminal kinase 1, serum/glucocorticoid-induced serine/threonine kinase), and a miscellaneous group (calmodulin, cyclin D2, LMO-4, metallothionein 3). Several other genes that were upregulated in waking and all the genes upregulated in sleep, with the exception of the one coding for membrane protein E25, did not match any known sequence. Thus, significant changes in gene expression occur across behavioral

states, which are likely to affect basic cellular functions such as RNA and protein synthesis, neural plasticity, neurotransmission, and metabolism

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 2

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(JNK1; gene expression in brain across the sleep-waking cycle)

IT Sleep
(nonrapid eye movement; gene expression in brain across the sleep-waking cycle)

IT Sleep
(rapid eye movement; gene expression in brain across the sleep-waking cycle)

IT 9026-09-9, Aryl sulfotransferase 149146-91-8, TrkB tyrosine receptor kinase 289898-51-7, JNK1 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression in brain across the sleep-waking cycle)

IT 289898-51-7, JNK1 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene expression in brain across the sleep-waking cycle)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 30 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:48639 HCAPLUS

DOCUMENT NUMBER: 130:76613

TITLE: Novel composition for treating, preventing and/or delaying ischemic cell death using proteins having the function of aFGF or activators of stress-activated protein kinases

INVENTOR(S): Schaper, Wolfgang; Htun, Patrik

PATENT ASSIGNEE(S): Max-Planck-Gesellschaft Zur Forderung Der Wissenschaften E.V., Germany

SOURCE: PCT Int. Appl., 51 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9901150	A1	19990114	WO 1998-EP4134	19980703 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HR, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9888557	A1	19990125	AU 1998-88557	19980703 <--

PRIORITY APPLN. INFO.:

US 1997-888112
WO 1998-EP4134A 19970703 <--
W 19980703 <--

ED Entered STN: 25 Jan 1999

AB Pharmaceutical compns. are provided comprising a protein having the biol. function of acidic fibroblast growth factor (aFGF) and/or a nucleic acid mol. encoding said protein having the biol. function of aFGF and/or an activator of stress - activated protein kinases (SAPK) and/or a nucleic acid mol. encoding said activator of SAPK which are particularly useful for treating, preventing and/or delaying ischemic cell death. Furthermore, methods for treating, preventing and/or delaying ischemic cell death comprising contacting organs, tissue or cells with a protein having the biol. function of aFGF and/or a nucleic acid mol. encoding said protein having the biol. function of aFGF and/or an activator of SAPKs and/or a nucleic acid mol. encoding said activator of SAPK are also described. The cell death is caused by a vascular disease or a cardiac infarct or a stroke. The vascular disease is arteriosclerosis, a coronary artery disease, a cerebral occlusive disease, a peripheral occlusive disease, a visceral occlusive disease, a mesenterial arterial insufficiency or an **ophthalmic** or retinal occlusion. The treatment method can also be used treating subjects before, during, or after exposure to an agent or radiation or surgical treatment that damages or destroys arteries.

IC ICM A61K038-18

ICS A61K031-40; A61K048-00

CC 2-5 (Mammalian Hormones)

Section cross-reference(s): 1

IT **Eye, disease**

(occlusion; composition for treating, preventing and/or delaying ischemic cell death using proteins having the function of aFGF or activators of stress-activated protein kinases)

IT **Eye, disease**

(retina, ischemia; composition for treating, preventing and/or delaying ischemic cell death using proteins having the function of aFGF or activators of stress-activated protein kinases)

IT 155215-87-5, **c-Jun N-terminal****kinase** 155215-87-5, Stress-activated protein kinase

172306-35-3, Stress-activated p46 protein kinase

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(activators; composition for treating, preventing and/or delaying ischemic cell death using proteins having the function of aFGF or activators of stress-activated protein kinases)

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L638 ANSWER 31 OF 94 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:330046 HCAPLUS

DOCUMENT NUMBER: 130:332886

TITLE: Use of sesquiterpene lactones for treatment of severe inflammatory disorders

INVENTOR(S): Hwang, Daniel H.; Fischer, Nikolaus H.

PATENT ASSIGNEE(S): Board of Supervisors of Louisiana State University and Agricultural and Mechanical College, USA

SOURCE: U.S., 15 pp.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5905089	A	19990518	US 1998-59480	19980413 <--
PRIORITY APPLN. INFO.:			US 1997-80224	A 19970414 <--

ED Entered STN: 28 May 1999

AB Sesquiterpene lactones are useful in suppressing the early proinflammatory cytokines, and in ameliorating septic shock and other severe inflammatory disorders. Sesquiterpene lactones with an α -methylene- γ -lactone functional group suppress the expression of the inducible cyclooxygenase-2 and proinflammatory cytokines [Interleukin-1 α and β , IL-1, and tumor necrosis factor- α (TNF α)] in mammalian macrophages stimulated with lipopolysaccharide. This suppression correlated with the inhibition of protein-tyrosine phosphorylation including the mitogen-activated protein kinases.

IC ICM A61K031-34

INCL 514468000

CC 1-7 (Pharmacology)
Section cross-reference(s): 63

IT AIDS (disease)
Anti-inflammatory agents
Anti-ischemic agents
Behcet's syndrome
Cytotoxic agents
Niemann-Pick disease
Psoriasis
Sepsis
Signal transduction, biological
(sesquiterpene lactones for treatment of severe inflammatory disorders)

IT 363-24-6, PGE2 9035-58-9, Blood-coagulation factor III 79747-53-8, Phosphotyrosine phosphatase 80449-02-1, Protein tyrosine kinase 83869-56-1, GM-CSF 137632-07-6, ERK 1 kinase 137632-08-7, ERK 2 kinase 142243-02-5, Mitogen-activated protein kinase 155215-87-5, **Protein kinase JNK1** 165245-96-5, P38 Kinase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sesquiterpene lactones for treatment of severe inflammatory disorders)

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L638 ANSWER 32 OF 94 USPATFULL on STN DUPLICATE 1

ACCESSION NUMBER: 2003:325471 USPATFULL

TITLE: SYSTEMS AND METHODS FOR CHARACTERIZING A BIOLOGICAL CONDITION OR AGENT USING PRECISION GENE EXPRESSION PROFILES

INVENTOR(S): Bevilacqua, Michael P., Boulder, CO, UNITED STATES
Bankaitis-Davis, Danute M., Longmont, CO, UNITED STATES
Cheronis, John C., Conifer, CO, UNITED STATES
Tryon, Victor, Loveland, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003229455	A1	20031211

APPLICATION INFO.: US 6692916 B2 20040217
 RELATED APPLN. INFO.: US 2001-821850 A1 20010329 (9) <--
 Continuation-in-part of Ser. No. US 2000-605581, filed
 on 28 Jun 2000, ABANDONED

	NUMBER	DATE	
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PRIORITY INFORMATION:	US 1999-141542P	19990628 (60)	<--
	US 2000-195522P	20000407 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	BROMBERG & SUNSTEIN LLP, 125 SUMMER STREET, BOSTON, MA, 02110-1618		
NUMBER OF CLAIMS:	166		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	49 Drawing Page(s)		
LINE COUNT:	3670		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			
AB	Methods are provided for evaluating a biological condition of a subject using a calibrated profile data set derived from a data set having a plurality of members, each member being a quantitative measure of the amount of a subject's RNA or protein as distinct constituents in a panel of constituents. The biological condition may be a naturally occurring physiological state or may be responsive to treatment of the subject with one or more agents. Calibrated profile data sets may be used as a descriptive record for an agent.		
IT	289898-51-7, JNK1 kinase (diagnosis and drug screening using calibrated gene expression profiles)		
RN	289898-51-7 USPATFULL		
CN	Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)		

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 33 OF 94 USPATFULL on STN DUPLICATE 2
 ACCESSION NUMBER: 2003:214408 USPATFULL
 TITLE: Inhibitors of c-Jun N terminal kinases (JNK) and other protein kinases
 INVENTOR(S): Green, Jeremy, Burlington, MA, UNITED STATES
 Bemis, Guy, Arlington, MA, UNITED STATES
 Grillot, Anne-Laure, Cambridge, MA, UNITED STATES
 Ledebroer, Mark, Acton, MA, UNITED STATES
 Salituro, Francesco G., Marlboro, MA, UNITED STATES
 Harrington, Edmund, South Boston, MA, UNITED STATES
 Gao, Huai, Natick, MA, UNITED STATES
 Baker, Christopher, Bedford, MA, UNITED STATES
 Cao, Jingrong, Newton, MA, UNITED STATES
 Hale, Michael, Bedford, MA, UNITED STATES

	NUMBER	KIND	DATE	
	-----	-----	-----	
PATENT INFORMATION:	US 2003149051	A1	20030807	
	US 6693108	B2	20040217	
APPLICATION INFO.:	US 2002-74177	A1	20020212 (10)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2000-US22445, filed on 11 Aug 2000, PENDING			

NUMBER	DATE
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PRIORITY INFORMATION: US 1999-148795P 19990813 (60) <--
 US 1999-166922P 19991122 (60) <--
 US 2000-211517P 20000614 (60) <--
 DOCUMENT TYPE: Utility
 FILE SEGMENT: APPLICATION
 LEGAL REPRESENTATIVE: VERTEX PHARMACEUTICALS INCORPORATED, 130 Waverly Street,
 Cambridge, MA, 02130-4646
 NUMBER OF CLAIMS: 24
 EXEMPLARY CLAIM: 1
 LINE COUNT: 2022
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB The present invention provides compounds of formula I: ##STR1##

where R^{sup.1} is H, CONH^{sub.2}, T^{sub.(n)}--R, or T^{sub.(n)}--Ar^{sup.2}, n may be zero or one, and G, XYZ, and Q are as described below. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

IT 289898-51-7, c-JUN N-terminal kinase
 (inhibitors; preparation of as isoxazolylpyrimidines and related compds. as inhibitors of c-JUN N-terminal kinases and other protein kinases)
 RN 289898-51-7 USPATFULL
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 34 OF 94 USPATFULL on STN DUPLICATE 3
 ACCESSION NUMBER: 2003:4081 USPATFULL
 TITLE: Antisense oligonucleotide compositions and methods for the modulation of JNK proteins
 INVENTOR(S): McKay, Robert, San Diego, CA, UNITED STATES
 Dean, Nicholas M., Olivenhain, CA, UNITED STATES
 Monia, Brett P., LaCosta, CA, UNITED STATES
 Nero, Pamela, San Diego, CA, UNITED STATES
 Gaarde, William A., Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003004120	A1	20030102
	US 6809193	B2	20041026
APPLICATION INFO.:	US 2001-774809	A1	20010131 (9) <--
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1999-396902, filed on 15 Sep 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-287796, filed on 7 Apr 1999, GRANTED, Pat. No. US 6133246 Continuation-in-part of Ser. No. US 1998-130616, filed on 7 Aug 1998, GRANTED, Pat. No. US 6221850 Continuation-in-part of Ser. No. US 1997-910629, filed on 13 Aug 1997, GRANTED, Pat. No. US 5877309		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Kathleen A. Tyrrell, LICATA & TYRRELL P.C., 66 E. Main Street, Marlton, NJ, 08053		
NUMBER OF CLAIMS:	33		
EXEMPLARY CLAIM:	1		

LINE COUNT: 4698

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a gene encoding a Jun N-terminal kinase (JNK protein) are provided. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other JNK proteins and specific isoforms thereof. Methods of treating animals suffering from diseases or disorders amenable to therapeutic intervention by modulating the expression of one or more JNK proteins with such oligonucleotide are also provided. Methods for the treatment and diagnosis of diseases or disorders associated with aberrant expression of one or more JNK proteins are also provided. Methods for inducing apoptosis and for treating diseases or conditions associated with a reduction in apoptosis are also provided.

IT 289898-51-7, JNK1

(antisense oligonucleotide compns. and methods for modulation of JNK proteins)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 35 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2005:208996 USPATFULL

TITLE: Novel splice variant of MyD88 and uses thereof

INVENTOR(S): Beyaert, Rudi, Zingem, BELGIUM
Janssens, Sophie, Gent, BELGIUM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005181476	A1	20050818
APPLICATION INFO.:	US 2004-888288	A1	20040709 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2003-EP381, filed on 10 Jan 2003, UNKNOWN		

	NUMBER	DATE	
PRIORITY INFORMATION:	EP 2002-75068	20020110	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	TRASK BRITT, P.O. BOX 2550, SALT LAKE CITY, UT, 84110, US		
NUMBER OF CLAIMS:	27		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	7 Drawing Page(s)		
LINE COUNT:	2186		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the field of infection and inflammation and, more specifically, to the field of pathogen-induced nuclear factor kappa B activation. More specifically, a novel splice variant of MyD88, (MyD88.sub.S), which has been identified encoding a protein that inhibits LPS-induced NF- κ B activation. MyD88.sub.S is a target to inhibit the phenomenon of endotoxin-tolerance that occurs in sepsis.

IT 289898-51-7, c-Jun N-terminal kinase

(pathway; sequence, biol. activities, and use as a medicament of human protein encoded by splice variant of MyD88 gene, including its ability activate JNK pathway and AP-1 dependent gene expression)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 36 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2005:152010 USPATFULL

TITLE: Antisense inhibition via RNase H-independent reduction
in mRNA

INVENTOR(S): Monia, Brett P., Encinitas, CA, UNITED STATES
Freier, Susan M., San Diego, CA, UNITED STATES
Manoharan, Muthiah, Weston, MA, UNITED STATES
Gaarde, William A., Carlsbad, CA, UNITED STATES
Griffey, Richard H., Vista, CA, UNITED STATES
Swayze, Eric E., Carlsbad, CA, UNITED STATES
Bennett, C. Frank, Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005130924	A1	20050616
APPLICATION INFO.:	US 2004-948947	A1	20040924 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2003-461163, filed on 13 Jun 2003, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-392020P	20020626 (60)
DOCUMENT TYPE:	Utility	<--
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	LICATA & TYRRELL P.C., 66 E. MAIN STREET, MARLTON, NJ, 08053, US	
NUMBER OF CLAIMS:	26	
EXEMPLARY CLAIM:	1	
LINE COUNT:	7167	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compositions and methods for reducing
levels of a preselected mRNA, using antisense compounds targeted to a
splice site or a region up to 50 nucleobases upstream of an exon/intron
junction on said mRNA. Preferably, said antisense compounds do not
elicit RNase H cleavage of the mRNA.

IT 289898-51-7, JNK1 kinase
(targeting mRNA of; splice site-binding antisense oligonucleotides for
RNase H-independent reduction in mRNA and proteins and their use in
treatment of cancer)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 37 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2005:87869 USPATFULL

TITLE: Novel compounds

INVENTOR(S): King, Sarah, Loughborough, UNITED KINGDOM
Teague, Simon, Loughborough, UNITED KINGDOM
Xue, Yafeng, Molndal, SWEDEN
Swahn, Britt-Marie, Sodertalje, SWEDEN

NUMBER	KIND	DATE
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PATENT INFORMATION: US 2005075334 A1 20050407
 APPLICATION INFO.: US 2004-499599 A1 20040617 (10) <--
 WO 2002-SE2374 20021218 <--

	NUMBER	DATE	
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PRIORITY INFORMATION:	SE 2001-4331	20011219	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	WHITE & CASE LLP, PATENT DEPARTMENT, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 10036		
NUMBER OF CLAIMS:	26		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2387		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to new compounds of formula (I) wherein R.sup.1, R.sup.2, R.sup.3, R.sup.4, R.sup.5 and A are defined as in formula (I), a process for their preparation and new intermediate prepared therein, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy, especially in the treatment of c-Jun N-terminal kinase (JNK) mediated conditions in mammals, particularly Alzheimer's Disease.

IT 289898-51-7, JNK1

(preparation of benzimidazole compds. as JNK inhibitors)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 38 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2005:69957 USPATFULL

TITLE: Systems and methods for characterizing a biological condition or agent using precision gene expression profiles

INVENTOR(S): Bevilacqua, Michael P., Boulder, CO, UNITED STATES
 Bankaitis-Davis, Danute M., Longmont, CO, UNITED STATES
 Cheronis, John C., Conifer, CO, UNITED STATES
 Tryon, Victor, Loveland, CO, UNITED STATES

	NUMBER	KIND	DATE	
	-----	-----	-----	
PATENT INFORMATION:	US 2005060101	A1	20050317	
APPLICATION INFO.:	US 2003-742458	A1	20031219 (10)	
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2002-291225, filed on 8 Nov 2002, PENDING Continuation-in-part of Ser. No. US 2001-821850, filed on 29 Mar 2001, GRANTED, Pat. No. US 6692916 Continuation-in-part of Ser. No. US 2000-605581, filed on 28 Jun 2000, ABANDONED			

	NUMBER	DATE	
	-----	-----	
PRIORITY INFORMATION:	US 2002-435257P	20021219 (60)	<--
	US 1999-141542P	19990628 (60)	<--
	US 2000-195522P	20000407 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	HEWLETT PACKARD COMPANY, P O BOX 272400, 3404 E. HARMONY ROAD, INTELLECTUAL PROPERTY ADMINISTRATION, FORT COLLINS, CO, 80527-2400		

NUMBER OF CLAIMS: 261
 EXEMPLARY CLAIM: 1
 NUMBER OF DRAWINGS: 49 Drawing Page(s)
 LINE COUNT: 5083

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method is provided in various embodiments for determining a profile data set for a subject with infectious disease or inflammatory conditions related to infectious disease based on a sample from the subject, wherein the sample provides a source of RNAs. The method includes using amplification for measuring the amount of RNA corresponding to at least 2 constituents from Table 1. The profile data set comprises the measure of each constituent, and amplification is performed under measurement conditions that are substantially repeatable.

IT 289898-51-7, Mitogen activated Protein Kinase 8
 (gene for, in diagnosis of infection or inflammation; gene expression profiles and markers for diagnosis of infection or inflammatory disease)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 39 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2005:31530 USPATFULL

TITLE: Inhibitors of c-jun N terminal kinases (JNK) and other protein kinases

INVENTOR(S): Green, Jeremy, Burlington, MA, UNITED STATES
 Bemis, Guy, Arlington, MA, UNITED STATES
 Grillot, Anne-Laure, Cambridge, MA, UNITED STATES
 Ledebor, Mark, Acton, MA, UNITED STATES
 Salituro, Francesco G., Marlboro, MA, UNITED STATES
 Harrington, Edmund, South Boston, MA, UNITED STATES
 Gao, Huai, Natick, MA, UNITED STATES
 Baker, Christopher, Bedford, MA, UNITED STATES
 Cao, Jingrong, Newton, MA, UNITED STATES
 Hale, Michael, Bedford, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005026967	A1	20050203
APPLICATION INFO.:	US 2004-779532	A1	20040213 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2002-74177, filed on 12 Feb 2002, GRANTED, Pat. No. US 6693108 Continuation of Ser. No. WO 2000-US22445, filed on 11 Aug 2000, PENDING		

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-148795P	19990813 (60)	<--
	US 1999-166922P	19991122 (60)	<--
	US 2000-211517P	20000614 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	VERTEX PHARMACEUTICALS INC., 130 WAVERLY STREET, CAMBRIDGE, MA, 02139-4242		
NUMBER OF CLAIMS:	24		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2164		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides compounds of formula I: ##STR1##

where R^{sup.1} is H, CONH^{sub.2}, T^(sub.n)--R, or T^(sub.n)--Ar^{sup.2}, n may be zero or one, and G, XYZ, and Q are as described below. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

IT 289898-51-7, c-JUN N-terminal kinase

(inhibitors; preparation of as isoxazolylpyrimidines and related compds. as inhibitors of c-JUN N-terminal kinases and other protein kinases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 40 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:299995 USPATFULL

TITLE: Jun kinase inhibitors

INVENTOR(S): Graczyk, Piotr, London, UNITED KINGDOM
Numata, Hiroshi, London, UNITED KINGDOM
Khan, Afzal, London, UNITED KINGDOM
Palmer, Vanessa, London, UNITED KINGDOM
Medland, Darren Peter, London, UNITED KINGDOM
Oinuma, Hitoshi, Tokyo-To, JAPAN
Bhatia, Gurpreet, London, UNITED KINGDOM

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004235864	A1	20041125		
APPLICATION INFO.:	US 2004-473578	A1	20040423	(10)	<--
	WO 2002-GB1598		20020404		<--

	NUMBER	DATE	
PRIORITY INFORMATION:	GB 2001-8770	20010406	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	WILMER CUTLER PICKERING HALE AND DORR LLP, THE WILLARD OFFICE BUILDING, 1455 PENNSYLVANIA AVE, NW, WASHINGTON, DC, 20004		
NUMBER OF CLAIMS:	58		
EXEMPLARY CLAIM:	1		
LINE COUNT:	2601		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

AB The present invention provides novel compounds of formula I ##STR1##

and their use in the inhibition of c-Jun N-terminal kinases. The present invention further provides the use of these compounds in medicine, in particular in the prevention and/or treatment of neurodegenerative disorders related to apoptosis and/or inflammation.

IT 289898-51-7, JNK1

(preparation of pyrroloimidazoles and imidazopyridines as Jun kinase inhibitors useful for preventing and/or treating certain neurodegenerative disorders)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 41 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:287280 USPATFULL

TITLE: Systems and methods for characterizing a biological
condition or agent using selected gene expression
profiles

INVENTOR(S): Bevilacqua, Michael P., Boulder, CO, UNITED STATES
Cheronis, John C., Conifer, CO, UNITED STATES
Tryon, Victor, Loveland, CO, UNITED STATES
Bankaitis-Davis, Danute M., Longmont, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004225449	A1	20041111
APPLICATION INFO.:	US 2004-781558	A1	20040217 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-821850, filed on 29 Mar 2001, GRANTED, Pat. No. US 6692916 Continuation-in-part of Ser. No. US 2000-605581, filed on 28 Jun 2000, ABANDONED		

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-141542P	19990628 (60)	<--
	US 2000-195522P	20000407 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Barbara J. Carter, Bromberg & Sunstein LLP, 125 Summer Street, Boston, MA, 02110-1618		
NUMBER OF CLAIMS:	6		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	49 Drawing Page(s)		
LINE COUNT:	3949		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods are provided for evaluating a biological condition of a subject
using a calibrated profile data set derived from a data set having a
plurality of members, each member being a quantitative measure of the
amount of a subject's RNA or protein as distinct constituents in a panel
of constituents. The biological condition may be a naturally occurring
physiological state or may be responsive to treatment of the subject
with one or more agents. Calibrated profile data sets may be used as a
descriptive record for an agent.

IT 289898-51-7, Mitogen activated protein kinase 8
(systems and methods for characterizing a biol. condition or agent
using calibrated gene expression profiles)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 42 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:173188 USPATFULL

TITLE: Identification, monitoring and treatment of disease and
characterization of biological condition using gene
expression profiles

INVENTOR(S): Bevilacqua, Michael, Boulder, CO, UNITED STATES

Cheronis, John C., Conifer, CO, UNITED STATES
Tryon, Victor, Loveland, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004133352	A1	20040708
APPLICATION INFO.:	US 2002-291225	A1	20021108 (10) <--
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-821850, filed on 29 Mar 2001, GRANTED, Pat. No. US 6692916		
	Continuation-in-part of Ser. No. US 2000-605581, filed on 28 Jun 2000, ABANDONED		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-348213P	20011109 (60) <--
	US 2001-340881P	20011207 (60) <--
	US 2002-369633P	20020403 (60) <--
	US 2002-376997P	20020430 (60) <--
	US 1999-141542P	19990628 (60) <--
	US 2000-195522P	20000407 (60) <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BROMBERG & SUNSTEIN LLP, 125 SUMMER STREET, BOSTON, MA, 02110-1618	
NUMBER OF CLAIMS:	77	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	44 Drawing Page(s)	
LINE COUNT:	4839	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Gene expression data, in particular gene expression profiles, are created and used in the identification, monitoring and treatment of disease and characterization of biological conditions. Profile data sets are derived from subject samples and include quantitative substantially repeatable measures of a distinct amount of RNA or protein constituent in a panel selected to enable evaluation of a biological condition. Such profile data sets may be used to provide an index indicative of the biological state of a subject, which may be compared to a normative value of the index determined with respect to a relevant population of subjects.

IT 289898-51-7, Mitogen-activated protein kinase 8
(Skin Response Gene Expression Panel; identification, monitoring and treatment of disease and characterization of biol. condition using gene expression profiles)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 43 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:166048 USPATFULL

TITLE: Novel 1h-indazole compound

INVENTOR(S): Oinuma, Hitoshi, Ibaraki, JAPAN
Ohi, Norihito, Ibaraki, JAPAN
Sato, Nobuaki, Ibaraki, JAPAN
Soejima, Motohiro, Ibaraki, JAPAN
Seshimo, Hidenori, Saitama, JAPAN
Terauchi, Taro, Ibaraki, JAPAN
Doko, Takashi, Ibaraki, JAPAN
Kohmura, Naohiro, Ibaraki, JAPAN

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004127538	A1	20040701		
APPLICATION INFO.:	US 2003-469399	A1	20030828	(10)	<--
	WO 2002-JP3735		20020415		<--

	NUMBER	DATE	
PRIORITY INFORMATION:	JP 2001-116521	20010416	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747		
NUMBER OF CLAIMS:	36		
EXEMPLARY CLAIM:	1		
LINE COUNT:	9144		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a novel 1H-indazole compound having an excellent JNK inhibitory action. More specifically, it provides a compound represented by the following formula, a salt thereof or a hydrate of them. ##STR1##

Wherein R.sup.1 is a C.sub.6-C.sub.14 aromatic cyclic hydrocarbon group etc.; R.sup.2, R.sup.4 and R.sup.5 each independently represent a hydrogen atom, a halogen atom, a cyano group etc.; L is a single bond, or a C.sub.1-C.sub.6 alkylene group etc.; X is a single bond, or a group represented by --CO--NH-- or --NH--CO--, etc.; and Y is a C.sub.3-C.sub.8 cycloalkyl group, a C.sub.6-C.sub.14 aromatic cyclic hydrocarbon group or a 5- to 14-membered aromatic heterocyclic group etc.

IT 289898-51-7, JNK1

(preparation of 1H-indazole derivs. as inhibitors of c-Jun amino-terminal kinase (JNK) and preventives and/or therapeutics for diseases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 44 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:127571 USPATFULL

TITLE: Concomitant drugs

INVENTOR(S): Ohkawa, Shinegori, Takatsuki-shi, JAPAN
Naruo, Kenichi, Sanda-shi, JAPAN
Miwatashi, Seiji, Ikeda-shi, JAPAN

	NUMBER	KIND	DATE		
PATENT INFORMATION:	US 2004097555	A1	20040520		
APPLICATION INFO.:	US 2003-451839	A1	20030625	(10)	<--
	WO 2001-JP11353		20011225		<--

	NUMBER	DATE	
PRIORITY INFORMATION:	JP 2000-396220	20001226	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Mark Chao, Takeda Pharmaceuticals North America Inc, Intellectual Property Department, Suite 500 475 Half		

JNK-I's

generally

(not specific)

Day Road, Lincolnshire, IL, 60069
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
LINE COUNT: 8688

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a pharmaceutical agent containing one or more kinds of a p38 MAP kinase inhibitor and/or a TNF- α production inhibitor and one or more kinds of drugs selected from the group consisting of (1) a non-steroidal antiinflammatory drug, (2) a disease-modifying anti-rheumatic drug, (3) an anti-cytokine drug, (4) an immunomodulator, (5) a steroid and (6) a c-Jun N-terminal kinase inhibitor in combination. This combination agent is useful as a prophylactic or therapeutic agent of the diseases such as rheumatism, arthritis and the like, and other diseases.

IT 289898-51-7, c-JUN N-terminal kinase

(inhibitors; combination drugs containing p38MAP kinase inhibitors and/or TNF- α production inhibitors with other specified agents)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 45 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:83490 USPATFULL

TITLE: Jnk inhibitor

INVENTOR(S): Ohkawa, Shigenori, Osaka, JAPAN
Naruo, Kenichi, Hyogo, JAPAN
Miwatashi, Seiji, Osaka, JAPAN
Kimura, Hiroyuki, Osaka, JAPAN
Kawamoto, Tomohiro, Osaka, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004063946	A1	20040401	
APPLICATION INFO.:	US 2003-470751	A1	20030730	(10) <--
	WO 2002-JP828		20020201	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	JP 2001-27570	20010202	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	TAKEDA PHARMACEUTICALS NORTH AMERICA, INC, INTELLECTUAL PROPERTY DEPARTMENT, 475 HALF DAY ROAD, SUITE 500, LINCOLNSHIRE, IL, 60069		

NUMBER OF CLAIMS: 41
EXEMPLARY CLAIM: 1
LINE COUNT: 7571

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a c-Jun N-terminal kinase inhibitor containing an azole compound (I) substituted by a nitrogen-containing aromatic group having substituent(s) (except a compound represented by the formula: ##STR1##

) or a salt thereof or a prodrug thereof.

IT 289898-51-7, JNK1 kinase

(preparation of azoles as JNK inhibitors)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA

INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 46 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2004:70605 USPATFULL

TITLE: Net, a transcription factor of the tcf family, as
regulator of angiogenic factor expressionINVENTOR(S): Wasylyk, Bohdan, Illkirch, FRANCE
Multon, Marie-Christine, Versailles, FRANCE
Ayadi, Abdelkader, Strasbourg, FRANCE
Zheng, Hong, Strasbourg, FRANCE

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004053833	A1	20040318
APPLICATION INFO.:	US 2003-415181	A1	20031003 (10) <--
	WO 2001-EP12987		20011023

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2000-402968	20001025 <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	ROSS J. OEHLER, AVENTIS PHARMACEUTICALS INC., ROUTE 202-206, MAIL CODE: D303A, BRIDGEWATER, NJ, 08807	
NUMBER OF CLAIMS:	65	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	25 Drawing Page(s)	
LINE COUNT:	3071	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the regulation of the activity of NET (ERP/SAP-2) protein and to compounds which modify or regulate NET protein activity. The invention further relates to methods of screening for agonists or antagonists of NET in order to identify new pro-angiogenic or anti-angiogenic compounds and to therapeutic uses of these compounds. The invention also relates to transgenic animals bearing mutations in NET gene.

IT 289898-51-7, JNK1 Kinase

(NET phosphorylation by; drug screening for effectors of human and mouse NET transcription factors in regulation of angiogenesis)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 47 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2003:257719 USPATFULL

TITLE: Novel compositions and methods for the identification, assessment, prevention and therapy of ovarian cancer

INVENTOR(S): Damokosh, Andrew I., West Hartford, CT, UNITED STATES
Iartchouk, Natalia, Wayland, MA, UNITED STATES
Stec, James II, Plymouth, MA, UNITED STATES
Clark, Edwin A., Ashland, MA, UNITED STATES
Lu, Karen, Houston, TX, UNITED STATES
Hartmann, Lynn, Rochester, MN, UNITED STATES

PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc. (U.S. corporation)

NUMBER	KIND	DATE
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PATENT INFORMATION: US 2003180770 A1 20030925
APPLICATION INFO.: US 2003-361112 A1 20030207 (10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-384042P	20020529 (60)	<--
	US 2002-355388P	20020208 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Theodore R. Allen, Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA, 02139		
NUMBER OF CLAIMS:	20		
EXEMPLARY CLAIM:	1		
LINE COUNT:	4470		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

AB The present invention is directed to the identification of markers that can be used to determine whether ovarian cancer is sensitive or resistant to a therapeutic agent. In particular, the present invention is directed to the use of certain combinations of markers, wherein the expression of the markers correlates with sensitivity or resistance to a therapeutic agent. Thus, by examining the expression of the individual markers of a marker set, also referred to as the expression profile of the marker set, it is possible to determine whether a therapeutic agent, or combination of agents, will be most likely to reduce the growth rate of the ovarian cancer.

IT 289898-51-7, Mitogen-activated protein kinase 8
(expressed gene markers for determining whether ovarian cancer is susceptible
or resistance to therapeutic agents)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 48 OF 94 USPATFULL on STN
ACCESSION NUMBER: 2003:146802 USPATFULL
TITLE: Inhibitors of c-Jun N-terminal kinases (JNK)
INVENTOR(S): Salituro, Francesco, Marlborough, MA, UNITED STATES
Bemis, Guy, Arlington, MA, UNITED STATES
Green, Jeremy, Burlington, MA, UNITED STATES
Fejzo, Jasna, Arlington, MA, UNITED STATES
Xie, Xiaoling, Cambridge, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003100549	A1	20030529	
APPLICATION INFO.:	US 2001-8277	A1	20011203 (10)	<--
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2000-US15248, filed on 2 Jun 2000, PENDING			

	NUMBER	DATE	
PRIORITY INFORMATION:	US 1999-137523P	19990603 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Tina Powers, VERTEX PHARMACEUTICALS INC., 130 Waverly Street, Cambridge, MA, 02139-4242		
NUMBER OF CLAIMS:	12		

EXEMPLARY CLAIM: 1

LINE COUNT: 758

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

IT 289898-51-7, c-JUN N-terminal kinase
(inhibitors; preparation of pyrimidinediones as inhibitors of c-JUN N-terminal kinases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 49 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2003:79103 USPATFULL

TITLE: Use of carboxy compounds such as 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride as anti-inflammatory agents

INVENTOR(S): De Bosscher, Karolien, Zottegem, BELGIUM
Berghe, Wim Vanden, Gentbrugge, BELGIUM
Haegeman, Guy, Balegem, BELGIUM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003055030	A1	20030320
APPLICATION INFO.:	US 2002-177987	A1	20020621 (10) <--
RELATED APPLN. INFO.:	Continuation of Ser. No. WO 2000-EP13347, filed on 21 Dec 2000, UNKNOWN		

	NUMBER	DATE
PRIORITY INFORMATION:	EP 1999-204433	19991221 <--
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	TRASKBRITT, PC, P.O. Box 2550, Salt Lake City, UT, 84110	
NUMBER OF CLAIMS:	8	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	6 Drawing Page(s)	
LINE COUNT:	1147	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the use of specific carboxy compounds, more specifically to the use of 2(4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride, in the treatment of inflammatory diseases. Part of the invention is also a composition, preferably a pharmaceutical composition, comprising as active ingredient at least 2 (4-acetoxyphenyl)-2-chloro-N-methyl-ethylammonium chloride together with (pharmaceutically) acceptable excipients.

IT 289898-51-7, p46JNK kinase
(phenethylamine derivs. to prevent and/or treat inflammatory diseases and inflammation associated disorders)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 50 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2002:206655 USPATFULL

TITLE: Inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases

INVENTOR(S): Ledebouer, Mark, Acton, MA, UNITED STATES
Salituro, Francesco, Marlboro, MA, UNITED STATES
Moon, Young-Choon, Lexington, MA, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002111353	A1	20020815	<--
APPLICATION INFO.:	US 2001-5133	A1	20011205 (10)	<--

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2000-251409P	20001205 (60)	<--
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Tina M. Powers, VERTEX PHARMACEUTICALS INCORPORATED, 130 Waverly Street, Cambridge, MA, 02139-4242		
NUMBER OF CLAIMS:	16		
EXEMPLARY CLAIM:	1		
LINE COUNT:	1446		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

AB The present invention provides compounds of formula I: ##STR1##

wherein G is a small group selected from hydrogen or C.sub.1-3 alkyl, Q is pyridine or pyrimidine, and R.sup.1-R.sup.3 are as defined in the specification. These compounds are selective JNK inhibitors showing good activity against the three isoforms of JNK (JNK1, JNK2 and JNK3) and relatively low activity against p38 kinase. The compounds are therefore useful for treating JNK-mediated diseases, especially neurodegenerative diseases in which all three JNK isoforms are implicated.

IT 289898-51-7, JNK1 protein kinase

(mediated disorders; treatment; preparation of pyrazolylpyridine- and -pyrimidineamines as JNK inhibitors)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 51 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2002:290942 USPATFULL

TITLE: Quinazoline derivatives as medicaments

INVENTOR(S): Chakravarty, Sarvajit, Sunnyvale, CA, United States
Dugar, Sundeep, Bridgewater, NJ, United States
Perumattam, John J., Los Altos, CA, United States
Schreiner, George F., Los Altos Hills, CA, United States
Liu, David Y., Palo Alto, CA, United States
Lewicki, John A., Los Gatos, CA, United States
PATENT ASSIGNEE(S): Scios, Inc., Sunnyvale, CA, United States (U.S. corporation)

NUMBER	KIND	DATE
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PATENT INFORMATION: US 6476031 B1 20021105 <--
APPLICATION INFO.: US 1999-383825 19990827 (9) <--
RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-141916, filed
on 28 Aug 1998, now patented, Pat. No. US 6184226
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Shah, Mukund J.
ASSISTANT EXAMINER: Liu, Hong
LEGAL REPRESENTATIVE: Morrison & Foerster LLP
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 1296
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention is directed to methods to inhibit TGF- β and/or
p38- α kinase using compounds of the formula ##STR1##

or the pharmaceutically acceptable salts thereof

wherein R.sup.3 is a noninterfering substituent;

each Z is CR.sup.2 or N, wherein no more than two Z positions in ring A
are N, and wherein two adjacent Z positions in ring A cannot be N;

each R.sup.2 is independently a noninterfering substituent;

L is a linker;

n is 0 or 1; and

Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic,
aromatic or heteroaromatic moiety optionally substituted with 1-3
noninterfering substituents.

IT 289898-51-7, JNK1
(inhibition of; preparation of quinazolines as TGF- β and/or p38- α
kinase inhibitors)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L638 ANSWER 52 OF 94 USPATFULL on STN

ACCESSION NUMBER: 2001:59871 USPATFULL

TITLE: Antisense oligonucleotide compositions and methods for
the modulation of JNK proteins

INVENTOR(S): McKay, Robert, La Mesa, CA, United States
Dean, Nicholas, Olivenhain, CA, United States
Monia, Brett P., La Costa, CA, United States
Nero, Pamela Scott, Oceanside, CA, United States
Gaarde, William A., Carlsbad, CA, United States

PATENT ASSIGNEE(S): Isis Pharmaceuticals Inc., Carlsbad, CA, United States
(U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6221850	B1	20010424	<--
APPLICATION INFO.:	US 1998-130616		19980807 (9)	<--
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1997-910629, filed on 13 Aug 1997, now patented, Pat. No. US 5877309			

DOCUMENT TYPE: Utility
 FILE SEGMENT: Granted
 PRIMARY EXAMINER: Brusca, John S.
 ASSISTANT EXAMINER: Shibuya, Mark L.
 LEGAL REPRESENTATIVE: Law Offices of Jane Massey Licata
 NUMBER OF CLAIMS: 23
 EXEMPLARY CLAIM: 1
 LINE COUNT: 3701

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a gene encoding a Jun N-terminal kinase (JNK protein) are provided. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other JNK proteins and specific isoforms thereof. Methods of treating animals suffering from diseases or disorders amenable to therapeutic intervention by modulating the expression of one or more JNK proteins with such oligonucleotide are also provided. Methods for the treatment and diagnosis of diseases or disorders associated with aberrant expression of one or more JNK proteins are also provided. The invention is thus directed to compositions for modulating, diagnostic methods for detecting, and therapeutic methods for inhibiting, the hyperproliferation of cells and formation, development and maintenance of tumors.

IT 289898-51-7, JNK1 kinase

(antisense oligonucleotides for JNK nucleic acids and their use as antitumor agents in mice, rats, and humans)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d iall abeq tech abex 53-76

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L638 ANSWER 53 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-553129 [53] WPIX

CROSS REFERENCE: 2004-553142 [53]

DOC. NO. CPI: C2004-202349

TITLE: New acyclic pyrazole compounds useful for treating e.g. connective tissue and joint disorders, neoplasia disorders, cardiovascular disorders, otic disorders and ophthalmic disorders.

DERWENT CLASS: B02 B03

INVENTOR(S): BUCHLER, I P; GRANETO, M J; HANAU, C E; HEGDE, S G; LIU, S; MERSHON, S M; MEYERS, M J; NACRO, K; WU, K K

PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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WO 2004058176	A2	20040715	(200453)*	EN	265	A61K000-00	
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RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
 LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE
 DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
 KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM
 PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US
 UZ VC VN YU ZA ZM ZW

US 2004152739 A1 20040805 (200453) A61K031-4439
 AU 2003301226 A1 20040722 (200476) A61K000-00
 AU 2003301226 A2 20040722 (200553) C07D401-04
 EP 1572682 A2 20050914 (200560) EN C07D401-14

R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
 MC MK NL PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004058176	A2	WO 2003-US40932	20031219
US 2004152739	A1 Provisional	US 2002-434962P	20021220 <--
		US 2003-742494	20031219
AU 2003301226	A1	AU 2003-301226	20031219
AU 2003301226	A2	AU 2003-301226	20031219
EP 1572682	A2	EP 2003-814309	20031219
		WO 2003-US40932	20031219

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003301226	A1 Based on	WO 2004058176
AU 2003301226	A2 Based on	WO 2004058176
EP 1572682	A2 Based on	WO 2004058176

PRIORITY APPLN. INFO: **US 2002-434962P**
20021220; US 2003-742494
 20031219

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-4439; C07D401-04; C07D401-14

SECONDARY: A61K031-415

BASIC ABSTRACT:

WO2004058176 A UPAB: 20050920

NOVELTY - Acyclic pyrazole compounds (I), are new.

DETAILED DESCRIPTION - Acyclic pyrazole compounds of formula (I).

Z1 = C;

Z2 - Z5 = C or N;

Z2+Z3 and Z4+Z5 = a pyrazole ring;

Ra = group of formula (i) - (iii);

a = single or double bonds;

M1 and M5 = C;

M2 - M4 and M6 = C, N, O or S;

Q1 and Q4 = C or N;

Q2, Q3 and Q5 = C, N, O or S;

X2 = O or N;

X1 = C;

X5 and X6 = N or C;

R1 = e.g. H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl;

R2 - R5 = absent or R1;

n = 0; and

R3+R4 = a ring of 5 - 8 atoms, where the atoms in the ring are independently selected from Z3, Z4, O, S, C=O, C=S, S=O, SO2, C (mono or di-substituted with R1), and N (optionally substituted with R1).

Full definitions are given in the DEFINITIONS (Full Definitions) section.

An INDEPENDENT CLAIM is included for a kit comprising a dosage form including compound (I).

ACTIVITY - Cytostatic; Cardiovascular-Gen.; **Ophthalmological**; Respiratory-Gen.; Gastrointestinal-Gen.; Antiangiogenic; Antiallergic; Antimicrobial; Endocrine-Gen.; Nephrotropic; Neuroprotective; Hepatotrophic; Antiinflammatory; Virucide; Muscular-Gen.; Gynecological; Vulnerary; Tranquilizer; Dermatological; Antianemic; Antiarthritic; Antirheumatic; Antigout; Osteopathic; Immunosuppressive; Antiasthmatic; Antipsoriatic; Antiulcer; Anti-HIV; Fungicide; Antimigraine; Analgesic; Antithyroid; Antipyretic; Antidiabetic; Cardiant; Vasotropic; CNS-Gen.; Nootropic; Hypotensive; Hypertensive; Antiarrhythmic; Thrombolytic; Antibacterial; Antiarteriosclerotic; Antianginal; Cerebroprotective; Anorectic; Antiinfertility; Antiparasitic; Antiparkinsonian; Eating-Disorder-Gen.; Antiaddictive; Antialcoholic; Neuroleptic; Antidepressant; Antismoking; Antiseborrheic; Anticonvulsant; Laxative; Auditory.

MECHANISM OF ACTION - Mitogen activated protein kinase-2 (MK-2) inhibitor.

1-(2-Aminoethyl)-3-(2-quinolin-3-yl-pyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate (A) was tested as inhibitor of MK2 kinase by measuring its effect on MK2 phosphorylation of peptide substrate. Recombinant MAPKAPK2 was phosphorylated at a concentration of 42 - 78 micro M by incubation with active p38a (0.23 micro M) in N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES) (50 mM), EDTA (0.1 mM), magnesium acetate (10 mM), and ATP (0.25 mM), pH 7.5 for one hour at 30 deg. C. The phosphorylation of HSP-peptide (KKKALSRQLSVAA) by MAPKAPK2 was measured using an anion exchange resin capture assay method. The reaction was initiated by the addition of MAPKAPK2 (15 nM) and was allowed to incubate at 30 deg. C for 30 minutes. The reaction was terminated and (gamma 33P)ATP was removed from solution by the addition of 150 micro l of AG 1X8 ion exchange resin in 900 mM sodium formate pH 3. A aliquot (50 micro l) of head volume was removed from the quenched reaction mixture and added to a 96-well plate, Microscint-40 (Packard) (150 micro l) was added and the amount of phosphorylated-peptide was determined. (A) showed IC50 value of 0.0269 mM.

USE - For preventing or treating a TNF- alpha mediated disease or disorder including connective tissue and joint disorder, neoplasia disorder, cardiovascular disorder, otic disorder, **ophthalmic** disorder, respiratory disorder, gastrointestinal disorder, angiogenesis related disorder, immunological disorder, allergic disorder, nutritional disorder, infectious disease and disorder, endocrine disorder, metabolic disorder, neurological and neurodegenerative disorder, psychiatric disorder, hepatic and biliary disorder, musculoskeletal disorder, genitourinary disorder, gynecologic and obstetric disorder, injury and trauma disorder, surgical disorder, dental and oral disorder, sexual dysfunction disorder, dermatologic disorder, hematological disorder, and poisoning disorder (e.g. arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, cancer, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylanhrosis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's

disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, **ophthalmic** diseases, retinitis, retinopathies, **conjunctivitis**, uveitis, **ocular** photophobia, acute injury to the **eye** tissue, pulmonary inflammation, viral infections, cystic fibrosis, central nervous system disorders, cortical dementia's, and Alzheimer's disease) in a mammal e.g. human (all claimed).

ADVANTAGE - The compounds are potent MK-2 inhibitors with an IC50 value for MK-2 of not more than 0.1 mM, and with reduced undesirable side effects, relative to p38 inhibitors.

Dwg.0/2

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-H; B07-D08; B14-A01; B14-A02; B14-A04B; B14-C02; B14-C03; B14-C04; B14-C09; B14-D06; B14-E10; B14-F01; B14-F02; B14-F03; B14-G03; B14-H01; B14-J01; B14-K01; B14-M01; B14-N01; B14-N02; **B14-N03**; B14-N05; B14-N06; B14-N07; B14-N10; B14-N11; B14-N12; B14-N14; B14-N17; B14-S01; B14-S04

TECH UPTX: 20040818

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation given.

Preferred Use: The neoplasia disorder includes Kaposi's sarcoma. The cardiovascular disorder includes hypertension, hypotension, heart arrhythmias, hypokalemia, cardiac ischemia, myocardial infarction, cardiac remodeling, cardiac fibrosis, myocardial necrosis, aneurysm, arterial fibrosis, embolism, constipation, vascular plaque inflammation, vascular plaque rupture, bacterial/viral inflammation, edema, swelling, fluid accumulation, cirrhosis of the liver, Bartter's syndrome, myocarditis, arteriosclerosis, atherosclerosis, calcification (such as vascular calcification), coronary artery disease, congestive heart failure, shock, left ventricular hypertrophy, angina, diabetic nephropathy, **eye** damage, vascular diseases, migraine headaches, aplastic anemia, diabetic cardiac myopathy, renal injury, renal arteriopathy, peripheral vascular disease, left ventricular hypertrophy, cognitive dysfunction, stroke, and headache. The metabolic disorder includes obesity, overweight, hypothyroidism, and hyperthyroidism. The respiratory disorder includes asthma, bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary edema, pulmonary embolism, pneumonia, pulmonary sarcoisosis, silicosis, pulmonary fibrosis, respiratory failure, acute respiratory distress syndrome and emphysema. The angiogenesis-related disorder includes angiofibroma, neovascular glaucoma, arteriovenous malformations, arthritis, osler-weber syndrome, atherosclerotic plaques, psoriasis, **corneal** graft neovascularization, pyogenic granuloma, delayed wound healing, retrolental fibroplasias, diabetic retinopathy, scleroderma, granulations, solid tumors, hemangioma, trachoma, hemophilic joints, vascular adhesions, hypertrophic scars, age-related macular degeneration, ulcers and infertility. The infectious disease includes rickettsial infections, chlamydial infections, parasitic infections and fungal infections. The neurodegenerative disorder include Parkinson's disease, dementia, senility, amyotrophy, ALS, amnesia, seizures, multiple sclerosis, muscular dystrophies, epilepsy, schizophrenia, depression, anxiety, attention deficit disorder, hyperactivity, bulimia, anorexia nervosa, anxiety, autism, phobias, spongiform encephalopathies, Creutzfeldt-Jakob disease, Huntington's Chorea, ischemia, obsessive-compulsive disorder, manic depression, bipolar disorders, drug addiction, alcoholism and smoking addiction. The dermatological disorders include acne, psoriasis, eczema, poison ivy, poison oak and dermatitis.

The otic disorders include otic pain, inflammation, otorrhea, otalgia, fever, otic bleeding, Lermoyez's syndrome, Meniere's disease, vestibular neuronitis, benign paroxysmal positional vertigo, herpes zoster oticus, Ramsay Hunt's syndrome.

ABEX

UPTX: 20040818

SPECIFIC COMPOUNDS - 7 Compounds are specifically claimed as (I) e.g. 1-(2-aminoethyl)-3-(2-quinolin-3-yl-pyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate (IA).

ADMINISTRATION - The compounds are administered in a dosage of 0.1 - 1500 (preferably 1 - 500, especially 10 - 400) mg/day/kg orally, parenterally (including subcutaneously, intramuscularly, intradermally, intramammary, intrasternally and intravenously).

EXAMPLE - To a cooled (0 degreesC) solution of ethyl 1-(2-aminoethyl)-3-(2-quinolin-3-ylpyridin-4-yl)-1H-pyrazole-5-carboxylate dihydrochloride (0.211 g) in anhydrous dimethyl formamide (DMF) (140 ml) was added lithium hydroxide (0.077 g) dropwise. The reaction was stirred for 30 minutes, then a solution of tert-butyl-2-bromoethylcarbamate (8.62 g) and sodium iodide (5.77 g) in anhydrous DMF (25 ml) was added dropwise. The reaction was stirred and warmed to room temperature for 20 hours. After work up 1-(2-aminoethyl)-3-(2-quinolin-3-yl-pyridin-4-yl)-1H-pyrazole-5-carboxylic acid trifluoroacetate (0.15 g, 69.4%) was obtained as a pink solid.

DEFINITIONS - Full Definitions: Preferably in (I):

Z1 = C;

Z2 - Z5 = C or N;

Z2+Z3 and Z4+Z5 = a pyrazole ring;

Ra = group of formula (i) - (iii);

a = single or double bonds;

M1 and M5 = C;

M2 - M4 and M6 = C, N, O or S;

Q1 and Q4 = C or N;

Q2, Q3 and Q5 = C, N, O or S;

X2 = O or N;

X1 = C;

X5 and X6 = N or C;

R1 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkyl-R11, 2-6C alkenyl-R11, 2-6C alkynyl-R11, 1-6C alkyl-(R11)2, 2-6C alkenyl-(R11)2, CSR11, amino, CONHR11, NHR7, NR8R9, N(R7)-N(R8)(R9), C(R11)=N-N(R8)(R9), N=N(R7), N(R7)-N=C(R8), C(R11)=N-O(R10), ON=C(R11), 1-6C alkyl-NHR7, 1-6C alkyl-NR8R9, (1-4C)alkyl-N(R7)N(R8)(R9), (1-4C)alkylC(R11)=N-N(R8)(R9), (1-4C)alkyl-N=N(R7), (1-4C)alkyl-N(R7)-N=C(R8), nitro, cyano, CO2R11, O-R10, 1-4C alkyl-OR10, COR11, SR10, SSR10, SOR11, SO2R11, 1-6C alkyl-COR11, 1-6C alkyl-SR10, 1-6C alkyl-SOR11, 1-6C alkyl-SO2R11, halo, Si(R11)3, halo 1-4C alkyl, or T1 (optionally substituted with R12);

T1 = (hetero)aryl, heterocyclyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, (hetero)arylalkyl, heterocyclylalkyl, or 1-10C mono- and bicyclic cycloalkyl;

R7 - R9 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-4C alkyl-R11, 1-6C alkyl-NHR13, 1-6C alkyl-NR13R14, O-R15, 1-6C alkyl-OR15, CO2R15, C(S)OR15, C(O)SR15, C(O)R17, C(S)R17, CONHR16, C(S)NHR16, CON(R16)2, C(S)N(R16)2, SR15, SOR17, SO2R17, 1-6C alkyl-CO2R15, 1-6C alkyl-C(S)OR15, 1-6C alkylC(O)SR15, 1-6C alkyl-COR17, 1-6C alkyl-C(S)R17, 1-6C alkyl-CONHR16, 1-6C alkyl-C(S)NHR16, 1-6C alkyl-CON(R16)2, 1-6C alkyl-C(S)N(R16)2, 1-6C alkyl-SR15, 1-6C alkyl-SOR17, 1-6C alkyl-SO2R17, halo 1-4C alkyl or T1 (optionally substituted with R18);

R10 = H, 1-10C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkyl-NHR13, 1-6C alkyl-NR13R14, 1-4C alkyl-OR15, CSR11, CO2R15, C(S)OR15, C(O)SR15, COR17, C(S)R17, CONHR16, 1-4C alkyl-R11, 1-4C alkyl-NH2R13, C(S)NHR16, O-R15, CON(R16)2, C(S)N(R16)2, SOR17, SO2R17, 1-6C alkyl-CO2R15, 1-6C

alkyl-C(S)OR15, 1-6C alkyl-C(O)SR15, 1-6C alkyl-COR17, 1-6C alkyl-C(S)R17, 1-6C alkyl-CONHR16, 1-6C alkylC(S)NHR16, 1-6C alkyl-CON(R16)2, Si(R13)2R17, 1-6C alkyl-C(S)N(R16)2, 1-6C alkyl-SR15, 1-6C alkyl-SOR17, 1-6C alkyl-SO2R17, halo 1-4C alkyl or T1 (optionally substituted with R18);

R11 = H, 1-6C alkyl, 1-6C alkoxy, 2-6C alkenyl, 2-6C alkynyl, amino, NHR13, NR13R14, N=NR13, 1-6C alkyl-NHR13, 1-6C alkyl-NR13R14, O-R15, 1-4C alkyl-OR15, SR15, COR13, CO2R17, 1-6C alkyl CO2R15, 1-6C alkyl-C(S)OR15, 1-6C alkyl-C(O)SR15, 1-6C alkyl-COR17, 1-6C alkyl-C(S)R17, 1-6C alkyl-CONHR16, 1-6C alkyl-C(S)NHR16, 1-6C alkyl-CON(R16)2, 1-6C alkyl-C(S)N(R16)2, 1-6C alkyl-SR15, 1-6C alkylSOR17, 1-6C alkyl-SO2R17, halo, halo 1-4C alkyl or T1 (optionally substituted with R18);

R12 = H, OH, oxo, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 1-10C alkyl-R11, 2-10C alkenyl-R11, 2-10C alkynyl-R11, 1-10C alkyl-(R11)2, 2-10C alkenyl-(R11)2, CSR11, hydroxyl 1-6C alkyl-R11, amino 1-4C alkyl-R7, amino, NHR7, NR8R9, N(R7)-N(R8)(R9), C(R11)=NN(R8)(R9), N=N(R7), N(R7)-N=C(R8), C(R11)=N-O(R10), ON=C(R11), 1-10C alkyl-NHR7, 1-10C alkyl-NR8R9, (1-10C)alkyl-N(R7)-N(R8)(R9), (1-10C)alkylC(R11)=N-N(R8)(R9), (1-10C)alkyl-N=N(R7), (1-10C)alkyl-N(R7)N=C(R8), SCN, NCS, 1-10C alkyl SCN, 1-10C alkyl NCS, nitro, cyano, OR10, 1-10C alkyl-OR10, COR11, CO2R11, SR10, SSR10, SOR11, SO2R11, 1-10C alkyl-COR11, 1-10C alkyl-SR10, 1-10C alkyl-SOR11, 1-10C alkyl-SO2R11, halo, Si(R11)3, halo 1-10C alkyl or T1 (optionally substituted with R18);

R13 and R14 = H, oxo, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-4C alkyl-R23, 1-6C alkyl-NHR19, 1-6C alkyl-NR19R20, O-R21, 1-4C alkyl-OR21, CO2R21, COR21, C(S)OR21, C(O)SR21, C(O)R23, C(S)R23, CONHR22, C(S)NHR22, CON(R22)2, C(S)N(R22)2, SR21, SOR23, SO2R23, 1-6C alkyl-CO2R21, 1-6C alkylC(S)OR21, 1-6C alkyl-C(O)SR21, 1-6C alkyl-COR23, 1-6C alkyl-C(S)R23, 1-6C alkyl-CONHR22, 1-6C alkyl-C(S)NHR22, 1-6C alkyl-CON(R22)2, 1-6C alkyl-C(S)N(R22)2, 1-6C alkyl-SR21, 1-6C alkyl-SOR23, 1-6C alkyl SO2R23, halo Ci-C4 alkyl or T1 (optionally substituted with R24);

R15 and R16 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkyl-NHR19, 1-6C alkyl-NR19R20, 1-4C alkyl-OR21, CSR11, CO2R22, COR23, CONHR22, CON(R22)2, SOR23, SO2R23, 1-6C alkyl-CO2R22, 1-6C alkyl-COR23, 1-6C alkyl-CONHR22, 1-6C alkyl-CON(R22)2, 1-6C alkyl-SR21, 1-6C alkyl-SOR23, 1-6C alkylSO2R23, halo Ci-C4 alkyl or T1 (optionally substituted with R24);

R17 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkenyl-R19, 1-6C alkyl-R19, 2-6C alkynyl, amino, NHR19, NR19R20, 1-6C alkylNHR19, 1-6C alkyl-NR19R20, O-R21, 1-4C alkyl-OR21, SR21, 1-6C alkylCO2R21, 1-6C alkyl-C(S)OR21, 1-6C alkyl-C(O)SR21, 1-6C alkyl-COR23, 1-6C alkyl-C(S)R23, 1-6C alkyl-CONHR22, 1-6C alkyl-C(S)NHR22, 1-6C alkyl-CON(R22)2, 1-6C alkyl-C(S)N(R22)2, 1-6C alkyl-SR21, 1-6C alkyl SOR23, 1-6C alkyl-SO2R23, halo Capproximately-C4 alkyl or T1 (optionally substituted with R24);

R18 = H, oxo, OH, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 1-10C alkyl-R23, 2-10C alkenyl-R23, 2-10C alkynyl-R23, 1-10C alkyl-(R23)2, 2-10C alkenyl-(R23)2, CSR23, amino, NHR19, NR20R20, N(R19)N(R20)(R20), C(R23)=N-N(R20)(R20), N=N(R19), N(R19)-N=C(R20), C(R23)=NO(R21), ON=C(R23), 1-10C alkyl-NHR19, 1-10C alkyl-NR20R20, (1-10C)alkyl-N(R19)-N(R20)(R20), (1-10C)alkylC(R23)=N-N(R20)(R20), (1-10C)alkyl-N=N(R19), (1-10C)alkyl-N(R19)-N=C(R20), SCN, NCS, 1-10C alkyl SCN, 1-10C alkyl NCS, nitro, cyano, O-R21, 1-10C alkyl-OR21, COR23, CO2R23, SR21, SSR21, SOR23, SO2R23, 1-10C alkyl-COR23, 1-10C alkyl-SR21, 1-10C alkyl-SOR23, 1-10C alkyl-SO2R23, halo, Si(R23)3, halo 1-10C alkyl or T1 (optionally substituted with R24);

R19 and R20 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-4C alkyl-R29, 1-6C alkyl-NHR25, 1-6C alkyl-NR25R26, O-R27, 1-4C alkyl-OR27, CO2R27, C(S)OR27, C(O)SR27, C(O)R29, C(S)R29, CONHR28, C(S)NHR28, CON(R28)2, C(S)N(R28)2, SR27, SOR29, SO2R29, 1-6C alkyl-CO2R27, 1-6C alkyl-C(S)OR27, 1-6C alkylC(O)SR27, 1-6C alkyl-COR29, 1-6C alkyl-C(S)R29, 1-6C

alkyl-CONHR28, 1-6C alkyl-C(S)NHR28, 1-6C alkyl-CON(R28)2, 1-6C alkyl-C(S)N(R28)2, 1-6C alkyl-SR27, 1-6C alkyl-SOR29, 1-6C alkyl-SO2R29, halo 1-4C alkyl or T1 (optionally substituted with R30);
R21 and R22 = H, 1-10C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkyl-NHR25, 1-6C alkyl-NR25R26, 1-4C alkyl-OR27, CSR11, CO2R28, COR29, CONHR28, CON(R28)2, SOR29, SO2R29, 1-6C alkyl-CO2R28, 1-6C alkyl-COR29, 1-6C alkyl-CONHR28, 1-6C alkyl-CON(R28)2, 1-6C alkyl-SR27, 1-6C alkyl-SOR29, 1-6C alkyl SO2R29, halo 1-4C alkyl or T1 (optionally substituted with R30);
R23 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkenyl-R25, 1-6C alkyl-R25, 2-6C alkynyl, amino, NHR25, NR25R26, 1-6C alkylNHR25, 1-6C alkyl-NR25R26, O-R27, 1-4C alkyl-OR27, SR27, 1-6C alkyl CO2R27, 1-6C alkyl-C(S)OR27, 1-6C alkyl-C(O)SR27, 1-6C alkyl-COR29, 1-6C alkyl-C(S)R29, 1-6C alkyl-CONHR28, 1-6C alkyl-C(S)NHR28, 1-6C alkyl-CON(R28)2, 1-6C alkyl-C(S)N(R28)2, 1-6C alkyl-SR27, 1-6C alkyl SOR29, 1-6C alkyl-SO2R29, halo 1-4C alkyl or T1 (optionally substituted with R30);
R24 = H, OH, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 1-10C alkyl-R29, 2-10C alkenyl-R29, 2-10C alkynyl-R29, 1-10C alkyl-(R29)2, 2-10C alkenyl-(R29)2, CSR29, amino, NHR25, NR26R26, N(R25)N(R26)(R26), C(R29)=N-N(R26)(R26), N=N(R25), N(R25)-N=C(R26), C(R29)=NO(R27), ON=C(R29), 1-10C alkyl-NHR25, 1-10C alkyl-NR26R26, (1-10C)alkyl-N(R25)-N(R26)(R26), (1-10C)alkylC(R29)=N-N(R26)(R26), (1-10C)alkyl-N=N(R25), (1-10C)alkyl-N(R25)-N=C(R26), SCN, NCS, 1-10C alkyl SCN, 1-10C alkyl NCS, nitro, cyano, O-R27, 1-10C alkyl-OR27, CO2R29, COR29, SR27, SSR27, SOR29, SO2R29, 1-10C alkyl-COR29, 1-10C alkyl-SR27, 1-10C alkyl-SOR29, 1-10C alkyl-SO2R29, halo, Si(R29)3, halo 1-10C alkyl, or T1 (optionally substituted with R30);
R25 and R26 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-4C alkyl-R35, 1-6C alkyl-NHR31, 1-6C alkyl-NR31R32, O-R33, 1-4C alkyl-OR33, CO2R33, C(S)OR33, C(O)SR33, C(O)R35, C(S)R35, CONHR34, C(S)NHR34, CON(R34)2, C(S)N(R34)2, SR33, SOR35, SO2R35, 1-6C alkyl-CO2R33, 1-6C alkyl-C(S)OR33, 1-6C alkylC(O)SR33, 1-6C alkyl-COR35, 1-6C alkyl-C(S)R35, 1-6C alkyl-CONHR34, 1-6C alkyl-C(S)NHR34, 1-6C alkyl-CON(R34)2, 1-6C alkyl-C(S)N(R34)2, 1-6C alkyl-SR33, 1-6C alkyl-SOR35, 1-6C alkyl-SO2R35, halo 1-4C alkyl, or T1 (optionally substituted with R36);
R27 and R28 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C alkyl-NHR31, 1-6C alkyl-NR31R32, 1-4C alkyl-OR33, CSR11, CO2R34, COR35, CONHR34, CON(R34)2, SOR35, SO2R35, 1-6C alkyl-CO2R34, 1-6C alkyl-COR35, 1-6C alkyl-CONHR34, 1-6C alkyl-CON(R34)2, 1-6C alkyl-SR33, 1-6C alkyl-SOR35, 1-6C alkylSO2R35, halo 1-4C alkyl or T1 (optionally substituted with R36);
R29 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkenyl-R31, 1-6C alkyl-R31, 2-6C alkynyl, amino, NHR31, NR31R32, 1-6C alkylNHR31, 1-6C alkyl-NR31R32, O-R33, 1-4C alkyl-OR33, SR33, 1-6C alkyl-CO2R33, 1-6C alkyl-C(S)OR33, 1-6C alkyl-C(O)SR33, 1-6C alkyl-COR35, 1-6C alkyl-C(S)R35, 1-6C alkyl-CONHR34, 1-6C alkyl-C(S)NH34, 1-6C alkyl-CON(R34)2, 1-6C alkyl-C(S)N(R34)2, 1-6C alkyl-SR33, 1-6C alkyl SOR35, 1-6C alkyl-SO2R35, halo 1-4C alkyl or T1 (optionally substituted with R36);
R30 = H, OH, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, 1-10C alkyl-R35, 2-10C alkenyl-R35, 2-10C alkynyl-R35, 1-10C alkyl-(R35)2, 2-10C alkenyl-(R35)2, CSR35, N=NR31, amino, NHR31, NR32R32, N(R31)-N(R32)(R32), C(R35)=N-N(R32)(R32), N=N(R31), N(R31)-N=C(R32), C(R35)=N-O(R33), ON=C(R35), 1-10C alkyl-NHR31, 1-10C alkylNR32R32, (1-10C)alkyl-N(R31)-N(R32)(R32), (1-10C)alkylC(R35)=NN(R32)(R32), (1-10C)alkyl-N=N(R31), (1-10C)alkyl-N(R31)-N=C(R32), SCN, NCS, 1-10C alkyl SCN, 1-10C alkyl NCS, nitro, cyano, O-R33, 1-10C alkyl-OR33, COR35, SR33, SSR33, SOR35, SO2R35, 1-10C alkyl-COR35, 1-10C alkyl-SR33, 1-10C alkyl-SOR35, 1-10C alkyl-SO2R35, halo, Si(R35)3, halo 1-10C alkyl or T1 (optionally substituted with R36);
R31 - R34 = H, alkyl, alkenyl, alkynyl, aminoalkyl, hydroxyalkyl,

alkylamino alkyl, dialkylaminoalkyl, alkoxyalkyl or T1 (optionally substituted with R36);
 R35 = R31, OH, alkoxy, amino, alkylamino or dialkylamino;
 R36 = H, alkyl, alkenyl, alkynyl, aminoalkyl, OH, alkoxy, amino, nitro, cyano, halo, alkylamino, dialkylamino, hydroxyalkyl, (di)alkylaminoalkyl, alkoxyalkyl, (hetero)aryl, heterocyclyl, cycloalkyl, alkylaryl, alkylheterocyclyl, alkylheteroaryl, heterocyclylalkyl, or (hetero)arylalkyl;
 R2 - R5, R37 and R38 = absent or R1;
 n = 0; and
 R3+R4 = a ring of 5 - 8 atoms, where the atoms in the ring are independently selected from Z3, Z4, O, S, C=O, C=S, S=O, SO2, C (mono or di-substituted with R1), and N (optionally substituted with R1).

L638 ANSWER 54 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-507272 [48] WPIX
 DOC. NO. CPI: C2004-187751
 TITLE: New enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide (I) and its salts and solvates, useful to treat/prevent diseases mediated by tumor necrosis factor-alpha and phosphodiesterase-4.
 DERWENT CLASS: B02
 INVENTOR(S): CHEN, R S; MULLER, G W
 PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004054501	A2	20040701	(200448)*	EN	56	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP							
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG							
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ							
VC VN YU ZA ZM ZW							
US 2004167199	A1	20040826	(200457)			A61K031-4035	
AU 2003294312	A1	20040709	(200474)			A61K000-00	
EP 1569599	A2	20050907	(200559)	EN		A61K007-00	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004054501	A2	WO 2003-US36741	20031117
US 2004167199	A1 Provisional	US 2002-427380P	20021118 <--
		US 2003-715184	20031117
AU 2003294312	A1	AU 2003-294312	20031117
EP 1569599	A2	EP 2003-789795	20031117
		WO 2003-US36741	20031117

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003294312	A1 Based on	WO 2004054501

EP 1569599

A2 Based on

WO 2004054501

PRIORITY APPLN. INFO: US 2002-427380P

20021118; US 2003-715184

20031117

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K007-00; A61K031-4035

BASIC ABSTRACT:

WO2004054501 A UPAB: 20040728

NOVELTY - Enantiomerically pure (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide (I), substantially free of its (+) isomer, and its salts and solvates are new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for

(1) inhibition of tumor necrosis factor- alpha (TNF- alpha) production comprising contacting a cell which produces TNF- alpha with (I);

(2) inhibition of phosphodiesterase-4 (PDE4) activity comprising contacting PDE4 with (I);

(3) controlling cAMP levels in a cell comprising contacting the cell with (I);

(4) preparation of (I); and

(5) an enantiomerically pure salt of (-)-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate (II).

ACTIVITY - Antidiabetic; Ophthalmological; Cytostatic; Antiinflammatory; Immunosuppressive; Antiseborrheic; Dermatological; Antibacterial; Antiulcer; Fungicide; Virucide; Protozoacide; Anti-HIV; Antiarthritic; Antirheumatic; Tranquilizer; Vulnerary; Antiallergic; Vasotropic; Antianemic; Antisickling; Osteopathic; Cardiovascular-Gen.; CNS-Gen.; Gastrointestinal-Gen.; Cerebroprotective; Nephrotropic; Antiangiogenic; Respiratory-Gen.; Antidepressant; Antiasthmatic; Antipsoriatic; Muscular-Gen.; Immunomodulator; Neuroprotective; Litholytic; Keratolytic; Hemostatic; Nootropic; Antiparkinsonian; Cardiant; Antimalarial; Thrombolytic; Antimicrobial; Antipyretic; Analgesic;

MECHANISM OF ACTION - TNF alpha inhibitor; PDE-4 inhibitor. (I) was tested for its ability to inhibit Lipopolysaccharide-induced TNF- alpha production from human peripheral blood mononuclear cells. The results showed that the median inhibitory concentration of (I) was 3 mu M (21 mu M for the control).

USE - (I) is useful to inhibit TNF alpha in mammalian (preferably human) cells and to treat or prevent diseases or disorders ameliorated by reduction of TNF- alpha levels (preferably diabetic retinopathy, retinopathy of prematurity, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic keratoconjunctivitis, atopic keratitis, superior limbic keratitis, pterygium keratitis sicca, Sjogrens, acne rosacea, phlyctenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegeners sarcoidosis, scleritis, Steven's Johnson disease, periphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Pagets disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Behcet's disease, retinitis, chproiditis, presumed ocular histoplasmosis, Bests disease, Stargarts disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting,

meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia or 5q-syndrome) or cancer (preferably a solid or blood-borne tumor (particularly solid tumors of the breast, colon, rectum, colorectum, kidney or gliomas), multiple myeloma, acute leukemia, lymphoblastic leukemia, myelogenous leukemia, lymphocytic leukemia or myelocytic leukemia). (I) is also useful to treat/prevent diseases/disorders ameliorated by PDE4 inhibition (preferably chronic obstructive pulmonary disease) and to treat depression, asthma, inflammation, inflammatory skin disease, psoriasis, atopic dermatitis, contact dermatitis, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, inflammatory bowel disease, Crohn's disease, colitis, chronic bronchitis, allergic rhinitis, arthritis, joint inflammation, ulcerative colitis, atopic eczema, stroke, bone resorption disease, multiple sclerosis, urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis, arthritic condition, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever, myalgia, malaria, HIV, AIDS, (AIDS related complex ARC), cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukemia, tarditive dyskinesia, yeast infection, fungal infection, conditions requiring gastroprotection, pain, myelodysplastic syndrome, myeloproliferative disease, macular degeneration and neurogenic inflammatory disease associated with irritation or pain. (All claimed.)

Dwg. 0/1

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; DCN
 MANUAL CODES: CPI: B06-D03; B10-B02G; B14-A01; B14-A02; B14-A03;
 B14-A04; B14-C01; B14-C02; B14-C03; B14-C09;
 B14-D07C; B14-E08; B14-E10C; B14-F01B; B14-F02;
 B14-F02D1; B14-F03; B14-F06; B14-G02; B14-H01;
 B14-J01A1; B14-J01A3; B14-J01A4; B14-K01; B14-L06;
B14-N03; B14-N04; B14-N06; B14-N16; B14-N17;
 B14-S01; B14-S04; B14-S06

TECH UPTX: 20040728

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) comprises contacting (R)-3-amino-3-(3,4-dimethoxyphenyl)propionic acid with phthalic dicarboxaldehyde to form (R)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionic acid, which is then reduced to form (I). Preferred Process: Methyl 3-amino-3-(3,4-dimethoxyphenyl)-propionate is contacted with a chiral amino acid to form the chiral amino acid salt (preferably N-acetyl-L-phenylalanine) of (R)-methyl 3-amino-3-(3,4-dimethoxyphenyl)-propionate, which is contacted with methylene chloride and tetrahydrofuran to form (R)-3-amino-3-(3,4-dimethoxyphenyl)propionic acid. Preferred Components: The enantiomerically pure salt of (I) is a chiral amino acid salt (preferably the L-isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid,

3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, N-acetyl-phenylalanine or N-acetyl-leucine). (II) is a chiral amino acid salt (preferably (-)-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate N-acetyl-L-phenylalanine salt).

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Process: Inhibition of TNF-alpha further comprises administration of an alkylating agent, nitrogen mustard, C-Jun kinase (JNK) inhibitor, antibiotic, antineoplastic agent, ethylenimine, methylmelamine alkyl sulfonate, nitrosourea, triazene, folic acid analog, pyrimidine analog, purine analog, vinca alkaloid, epipodophyllotoxin, steroid, topoisomerase inhibitor or anti-cancer vaccine. Treatment with (I) may further comprise administration of an antihistamine, anti-inflammatory drug, non-steroid anti-inflammatory drug, steroid, anti-cancer agent, hematopoietic growth factor, cytokine, stem cell transplantation, or kinase inhibitor.

ABEX UPTX: 20040728

ADMINISTRATION - Administration of (I) is 1-5000 (preferably 100-1200) mg/day in two doses, parenterally, transdermally, mucosally, nasally, buccally, sublingually, topically or orally (all claimed).

EXAMPLE - A 3-necked round bottom flask equipped with a mechanical stirrer and thermometer was charged with (R)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydroisoindol-2-yl)-propionic acid (32.6 g, 0.096 mol), THF (320 ml) and CDI (23.2 g, 0.143 mol). The resulting mixture was stirred at ambient temperature for 3 hours. Gaseous ammonia was introduced slowly into the reaction vessel for 30 minutes while the reaction temperature was maintained below 25degreesC. The resulting slurry was stirred at ambient temperature for another 2 hours. The mixture was concentrated to generate about 250 ml of distillate, then charged with distilled water (320 ml) and concentrated again to generate another portion of distillate (about 100 ml). The slurry was then filtered and the filter cake was washed with distilled water. The solid was air-dried and then dried in vacuo at 55degreesC to a constant weight, affording 30.0 g (92% yield) of (-)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide.

L638 ANSWER 55 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-431821 [40] WPIX
 DOC. NO. CPI: C2004-161740
 TITLE: Composition useful for treatment of e.g. diabetes, cancer, AIDS, depression and inflammation comprises (+)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionamide.
 DERWENT CLASS: B02 B05
 INVENTOR(S): CHEN, R S; MULLER, G W
 PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP
 COUNTRY COUNT: 107
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004045597	A1	20040603	(200440)*	EN	54	A61K031-24	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP							
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG							
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ							

VC VN YU ZA ZM ZW
 AU 2003294311 A1 20040615 (200470) A61K031-24

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004045597	A1	WO 2003-US36740	20031117
AU 2003294311	A1	AU 2003-294311	20031117

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003294311	A1 Based on	WO 2004045597

PRIORITY APPLN. INFO: **US 2002-427379P**
20021118

INT. PATENT CLASSIF.:

MAIN: A61K031-24
 SECONDARY: A61K031-40; C07C205-00; C07D209-34

BASIC ABSTRACT:

WO2004045597 A UPAB: 20040624

NOVELTY - A composition comprises (+)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionamide (I), its salt or solvate and carrier, excipient or diluent.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) preparation of (I) involves: a) reacting (S)-3-amino-3-(3,4-dimethoxyphenyl)propionic acid (a1) with phthalic dicarboxaldehyde under specified conditions to form (S)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionic acid (b1); and b) reducing (b1) under specified conditions to form (I);

(2) pure (+)-3-(3,4-dimethoxy-phenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)-propionamide, substantially free of its (-) isomer;

(3) Treatment (T1) of disease or disorder ameliorated by reduction of levels of tumor necrosis factor alpha (TNF- alpha) and cancer involving administration of (I); and

(4) Treatment (T2) of disease or disorder ameliorated by inhibition of phosphodiesterase type 4 (PDE4) involving administration of (I).

ACTIVITY - Analgesic; **Ophthalmological**; Antidiabetic; Immunosuppressive; Cytostatic; Antiinflammatory; Antiseborrheic; Dermatological; Antibacterial; Antiulcer; Fungicide; Virucide; Auditory; Protozoacide; Anti-HIV; Antiarthritic; Antirheumatic; Tranquilizer; Vulnerary; Osteopathic; Vasotropic; Neuroprotective; Respiratory-Gen.; Cerebroprotective; Antianemic; Antidepressant; Antiasthmatic; Antipsoriatic; Gastrointestinal-Gen.; Antiallergic; **Keratolytic**; Nootropic; Cardiant; Antimalarial; Antipyretic; Immunomodulator; Vulnerary; Nephrotropic; Muscular-Gen.

MECHANISM OF ACTION - TNF- alpha production inhibitor; PDE4 activity inhibitor.

USE - For inhibition of TNF-alpha production in cell (mammalian cell e.g. human cell); For treating or preventing disease or a disorder ameliorated by reduction of levels of TNF- alpha and by the inhibition of PDE4; For treating or preventing myelodysplastic syndrome, myeloproliferative disease, pain, macular degeneration, diabetic retinopathy, retinopathy of prematurity, **corneal** graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic **keratoconjunctivitis**, atopic **keratitis**, superior limbic

keratitis, pterygium keratitis sicca, Sjogren's, syndrome, acne rosacea, phlyctenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Kaposi sarcoma, Mooren ulcer, Terrien's marginal degeneration, marginal keratolysis, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegener's sarcoidosis; scleritis, Stevens-Johnson disease, periphigoid radial keratotomy, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eale's disease, Behcet's disease, retinitis, choroiditis, presumed ocular histoplasmosis, Best's disease, Stargart's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia and 5q- syndrome, cancer (e.g. solid tumor (e.g. tumor of breast, colon, rectum, colorectum, kidney and glioma), blood borne tumor, multiple myeloma, acute leukemia, lymphoblastic leukemia, myelogenous leukemia, lymphocytic leukemia, or myelocytic leukemia), depression, asthma, inflammation, inflammatory skin disease, psoriasis, atopic dermatitis, contact dermatitis, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, inflammatory bowel disease, Crohn's disease, colitis, chronic bronchitis, allergic rhinitis, arthritis, joint inflammation, ulcerative colitis, atopic eczema, stroke, bone resorption disease, multiple sclerosis, urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis, arthritic condition, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs. host reaction, allograft rejection, infection-related fever, myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type I diabetes mellitus, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukemia, tarditive dyskinesia, yeast infection, fungal infection, condition requiring gastroprotection and neurogenic inflammatory disease associated with irritation or pain; and for controlling cAMP levels in a cell (all claimed).

ADVANTAGE - The composition exhibits desire pharmacological properties more potently, more selectively and perhaps without unwanted or toxic affects.

Dwg.0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; DCN
MANUAL CODES:	CPI: B06-D01; B06-D03; B06-D04; B12-M11; B14-A01; B14-A01A2; B14-A02A3; B14-A02B1; B14-A03; B14-A03B; B14-A04; B14-C01; B14-C02; B14-C03; B14-C04; B14-C09; B14-C09A; B14-C09B; B14-D02B; B14-D03; B14-E08; B14-E10C; B14-E11; B14-F01B; B14-F02B2; B14-F02D; B14-F02D1; B14-F03; B14-F05; B14-G02; B14-G02C; B14-G02D; B14-H01; B14-H01A; B14-H01B; B14-J01A3; B14-J01A4; B14-J01B; B14-J05; B14-J05B; B14-K01; B14-K01F; B14-L06; B14-N01; B14-N03

; B14-N04; B14-N06B; B14-N10; B14-N16; B14-N17;
B14-N17B; B14-N17C; B14-S01; B14-S04; B14-S06

TECH

UPTX: 20040624

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compound: The pure salt of (I) is chiral amino acid salt selected from D isomer of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, ornithine, 4-aminobutyric acid, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, tert-butylglycine, tert-butylalanine, phenylglycine, cyclohexylalanine, N-acetyl-phenylalanine or N-acetyl-leucine (preferably N-acetyl-D-phenylalanine). Preferred Method: Reacting a chiral amino acid salt of (S)-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate (c1) with methylene chloride and tetrahydrofuran under conditions to form (a1). Reacting methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate with a chiral amino acid under condition to form (c1).

Preferred Composition: (T1) further involves administration of an alkylating agent, nitrogen mustard, JNK inhibitor, antibiotic, antineoplastic agent, ethylenimine, methylmelamine alkyl sulfonate, nitrosourea, triazene, folic acid analog, pyrimidine analog, purine analog, vinca alkaloid, epipodophyllotoxin, steroid, topoisomerase inhibitor or anti-cancer vaccine. (T2) further involves administration of antihistamine, anti-inflammatory drug, non-steroid anti-inflammatory drug, steroid anti-cancer drug, hematopoietic growth factor, cytokine, stem cell transplantation or kinase inhibitor.

ABEX

UPTX: 20040624

SPECIFIC COMPOUNDS - The use of (+)-methyl 3-amino-3-(3,4-dimethoxyphenyl)propionate N-acetyl-D-phenylalanine salt as (c1) is specifically claimed.

ADMINISTRATION - The composition is administrated in the dosage of 1 - 5000 (preferably 10 - 2500, especially 100 - 1200) mg/day or twice a day and administered parenterally, transdermally, mucosally, nasally, buccally, sublingually, topically or orally (claimed). Also administered subcutaneously, intravenously, intramuscularly, by bolus injection, intraarterially, vaginally or rectally.

EXAMPLE - A composition comprises (mg/tablet): (+)-3-(3,4-dimethoxyphenyl)-3-(1-oxo-1,3-dihydro-isoindol-2-yl)propionamide (100), microcrystalline cellulose (133.75), Pluronic F-68 (RTM; surfactant) (10), Croscarmellose sodium type A (5) and magnesium stearate (1.25).

L638 ANSWER 56 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-295308 [27] WPIX
DOC. NO. CPI: C2004-112977
TITLE: New imidazo(1,2-a)pyrazines useful in the treatment of
e.g. cancer, atherosclerosis, pulmonary fibrosis,
arthritis, psoriasis, glomerulonephritis.
DERWENT CLASS: B02
INVENTOR(S): DOLL, R J; DWYER, M P; GIRIJAVALLABHAN, V M; GUZI, T J;
PARUCH, K
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP
COUNTRY COUNT: 107
PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG MAIN IPC
WO 2004026310	A1 20040401	(200427)*	EN	46 A61K031-5025

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
 LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
 KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
 PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC
 VN YU ZA ZM ZW
 US 2004072835 A1 20040415 (200427) A61K031-498
 AU 2003275031 A1 20040408 (200462) A61K031-5025
 EP 1542693 A1 20050622 (200541) EN A61K031-5025
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
 MC MK NL PT RO SE SI SK TR

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004026310	A1	WO 2003-US29456	20030919
US 2004072835	A1 Provisional	US 2002-412906P	20020923 <--
		US 2003-666424	20030919
AU 2003275031	A1	AU 2003-275031	20030919
EP 1542693	A1	EP 2003-759300	20030919
		WO 2003-US29456	20030919

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003275031	A1 Based on	WO 2004026310
EP 1542693	A1 Based on	WO 2004026310

PRIORITY APPLN. INFO: US 2002-412906P

20020923; US 2003-666424
 20030919

INT. PATENT CLASSIF.:

MAIN: A61K031-498; A61K031-5025

SECONDARY: A61K031-407; A61K031-4406; A61K031-4427; C07D487-04

BASIC ABSTRACT:

WO2004026310 A UPAB: 20040426

NOVELTY - Imidazo(1,2-a)pyrazines are new.

DETAILED DESCRIPTION - Imidazo(1,2-a)pyrazines of formula (I) are new.

R = alkyl, arylalkyl, (hetero)aryl, cycloalkyl, heterocyclyl, Q (optionally substituted by T1, OR6, C(O)R7, CO2R6, -(CHR5)nOR6, S(O)2R7), CF3, heteroarylalkyl, cycloalkylalkyl, heterocyclylalkyl or C(O)R7;

Q = piperazin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, pyrrolidine-2-yl, piperidin-2-yl, pyrrolidine-3-yl, piperidin-4-yl, piperidin-3-yl or azepan-4-yl (all substituted by (R8)n);

T1 = halo, (cyclo)alkyl, CF3, CN, OCF3, NR5R6, C(O)NR5R6, SR6, S(O)2NR5R6, N(R5)S(O)2R7, N(R5)C(O)R7 or N(R5)C(O)NR5R6;

R1 = H, halo or alkyl;

R2 = H, halo, CN, cycloalkyl, alkyl, heterocyclyl, alkynyl or CF3;

R3 = (hetero)aryl, heterocyclyl (optionally substituted by T1, aryl, OR5, CO2R5, S(O)2R6), -(CHR5)n-heteroaryl, S(O)2R6, C(O)R6, S(O)2NR5R6, C(O)2R6, C(O)NR5R6, -(CHR5)n-T2, -(CH2)m-piperidinyl (substituted by R8 at 1 position);

T2 = pyrrolidin-2-one-1-yl, piperazin-1-yl (substituted by R8 at position 4);

R5 = H or alkyl;

R6 = (aryl)alkyl, (hetero)aryl, heteroarylalkyl (optionally

substituted by T1, aryl, OR5, CH2OR5, C(O)2R5, S(O)2R7) or H;
 R7 = (aryl)alkyl, (hetero)aryl, heteroarylalkyl (optionally
 substituted by T1, aryl, OR5, CH2OR5, C(O)2R5, S(O)2R7);

R8 = R6, C(O)NR5R6, S(O)2NR5R6, C(O)R7, C(O)2R6, S(O)2R7 or
 -(CH2)-aryl;

m = 0 - 4; and

n = 1 - 4.

Provided that

(1) when R3 is -(CHR5)n-heteroaryl, then R2 is alkyl; and

(2) R3 is not phenyl and furyl.

An INDEPENDENT CLAIM is included for treatment (t1) of cyclin
 dependent kinase associated diseases involving administering (I) or its
 salt or solvate and an anti-cancer agent.

ACTIVITY - Cytostatic; Neuroprotective; Antiarthritic; Nephrotropic;
 Antipsoriatic; Immunosuppressive; Antibacterial; Antiarteriosclerotic;
 Vulnerary; Vasotropic; Antiinflammatory; Respiratory-Gen.;
 Gastrointestinal-Gen.; Fungicide; Nootropic; Virucide; Anti-HIV;
 Dermatological; Antirheumatic; Antiparkinsonian; Antianemic;
 Cerebroprotective; Osteopathic; CNS-Gen.

MECHANISM OF ACTION - Cyclin dependent kinases (preferably
 (e.g. CDK2, **mitogen** activated protein kinase
 (MAPK/ERK), glycogen synthase kinase 3 (GSK3 beta)) inhibitor. Test
 results described but no results given.

USE - For the treatment of diseases e.g. cancer of the bladder,
 breast, colon, kidney, liver, lung, small cell lung, esophagus, gall
 bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, skin,
 squamous cell carcinoma, leukemia, acute lymphocytic leukemia, acute
 lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's
 lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, Burkett's lymphoma,
 acute and chronic myelogenous leukemia, myelodysplastic syndrome,
 promyelocytic leukemia, fibrosarcoma, rhabdomyosarcoma, astrocytoma,
 neuroblastoma, glioma, schwannomas, melanoma, seminoma, teratocarcinoma,
 osteosarcoma, xenoderoma, pigmentosum, **keratocanthoma**, thyroid
 follicular cancer or Kaposi's sarcoma (all claimed), benign prostate
 hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis,
 atherosclerosis, pulmonary fibrosis, arthritis, psoriasis,
 glomerulonephritis, restenosis following angioplasty or vascular surgery,
 hypertrophic scar formation, inflammatory bowel disease, transplantation
 rejection, endotoxic shock, fungal infections, Alzheimer's disease,
 apoptosis, viral infections (e.g. herpesvirus, poxvirus, Epstein- Barr
 virus, Sindbis virus and adenovirus), prevention of AIDS development in
 HIV-Infected individuals, autoimmune diseases (e.g. systemic lupus,
 erythematosis, autoimmune mediated glomerulonephritis, rheumatoid
 arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes
 mellitus), neurodegenerative disorders (e.g. Alzheimer's disease,
 AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis,
 retinitis pigmentosa, spinal muscular atrophy and cerebellar
 degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury
 associated with myocardial infarctions, stroke and reperfusion injury,
 arrhythmia, atherosclerosis, toxin-induced or alcohol related liver
 diseases, hematological diseases (e.g. chronic anemia and aplastic
 anemia), degenerative diseases of the musculoskeletal system (e.g.
 osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic
 fibrosis, multiple sclerosis, kidney diseases and cancer pain.

ADVANTAGE - The compounds have potent cyclin dependent kinase
 inhibiting activity.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B01-B01; B01-B02; B01-C03; B01-C05; B01-D02; B02-D;

B04-C01B; B05-A03B; B05-B01J; B05-B01M; B05-C05;
 B06-D08; B06-H; B07-H; B08-D02; B10-A10; B10-A13B;
 B10-A19; B10-B02A; B10-B02E; B10-B03B; B10-B04B;
 B10-E02; B10-H02E; B14-A02; B14-A04; B14-C03;
 B14-C06; B14-C09; B14-D06; B14-F01A; B14-F01E;
 B14-F01G; B14-F03; B14-F05; B14-F07; B14-G01;
 B14-G02C; B14-G02D; B14-H01; B14-H04; B14-J01A3;
 B14-J01A4; B14-K01; B14-L06; B14-N01;
 B14-N03; B14-N07A; B14-N10; B14-N12;
 B14-N16; B14-N17C; B14-S01; B14-S04

TECH UPTX: 20040426

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: No general preparation given.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The anti-cancer agent is cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11 (RTM; topoisomerase I inhibitor), irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methotrexate, 5FU, temozolomide, cyclophosphamide, SCH 66336 (RTM), R115777 (RTM), L778123 (RTM), BMS 214662 (RTM), iressa, tarceva, antibodies to EGFR, gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, uracil mustard, chlormethine, ifosfamide, melphalan, chlorambucil, pipobroman, triethylenemelamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN (RTM), pentostatine, vinblastin, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mithramycin, deoxycoformycin, mitomycin-C, L-Asparaginase, teniposide 17alpha-ethinylestradiol, diethylstilbestrol, testosterone, prednisone, fluoxymesterone, dromostanolone propionate, testolactone, megesterolacetate, methylprednisolone, methyltestosterone, prednisolone, triamcinolone, chlorotrianisene, hydroxyprogesterone, aminoglutethimide, estramustine, medroxyprogesteroneacetate, leuprolide, flutamide, toremifene, goserelin, cisplatin, carboplatin, hydroxyurea, amacrine, procarbazine, mitotane, mitoxantrone, levamisole, navelbene, anastrozole, letrozole, capecitabine, Reloxafine, droloxafine or hexamethylmelamine. Preferred Method: (t1) further involves a radiation therapy.

ABEX UPTX: 20040426

SPECIFIC COMPOUNDS - Ten compounds are specifically claimed as (I) e.g. 8-((3-pyridinylmethyl)amino)-6-methyl-imidazo(1,2-a)pyrazine (Ia).

ADMINISTRATION - (I) is administered in a dosage of 0.001 - 500 (especially 0.01 - 25) mg/kg of body weight/day. Administration is oral (1 - 500 (preferably 1 - 200) mg/day), parenteral, intranasal, by inhalation, transdermal, subcutaneous.

EXAMPLE - A mixture of 6-methyl-8-chloro-imidazo(1,2-a)pyrazine (1 equivalent (eq.)), 3-(aminomethyl)pyridine (1.1 eq.) and diisopropylethylamine (20 eq.) in anhydrous dioxane was stirred at 90degreesC under N2 for 48 hours. The solvent was evaporated and residue was purified to obtain pure 8-(3-pyridinylmethylamino)-6-methyl-imidazo(1,2-a)pyrazine (Ia).

DEFINITIONS - Preferred Definitions:

R = CH3, ethyl, tert-butyl, cyclohexylmethyl, benzyl or phenethyl;

R1 = H or CH3;

R2 = Br;

R3 = (pyrid-2-yl)methyl, (pyrid-3-yl)methyl, (pyrid-4-yl)methyl;

R5 = H or lower alkyl;

m = 0; and

n = 1.

L638 ANSWER 57 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-238720 [22] WPIX
 DOC. NO. CPI: C2004-093381
 TITLE: New 2,6-disubstituted 7-oxo-pyrido(2,3-d)pyrimidines
 useful for the treatment of p38 mediated disorder e.g.
 rheumatoid arthritis.
 DERWENT CLASS: B02
 INVENTOR(S): GOLDSTEIN, D M; LIM, J A
 PATENT ASSIGNEE(S): (GOLD-I) GOLDSTEIN D M; (LIMJ-I) LIM J A; (HOFF) HOFFMANN
 LA ROCHE & CO AG F
 COUNTRY COUNT: 104
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004014907	A1	20040219	(200422)*	EN	53	C07D471-04	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA							
ZM ZW							
US 2004038999	A1	20040226	(200422)			A61K031-519	
AU 2003251661	A1	20040225	(200456)			C07D471-04	
EP 1539755	A1	20050615	(200539)	EN		C07D471-04	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							
BR 2003013297	A	20050621	(200542)			C07D471-04	
US 2005203300	A1	20050915	(200561)			C07D471-02	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004014907	A1	WO 2003-EP8357	20030729
US 2004038999	A1 Provisional	US 2002-401491P	20020806 <--
		US 2003-634936	20030805
AU 2003251661	A1	AU 2003-251661	20030729
EP 1539755	A1	EP 2003-784102	20030729
		WO 2003-EP8357	20030729
BR 2003013297	A	BR 2003-13297	20030729
		WO 2003-EP8357	20030729
US 2005203300	A1 Provisional	US 2002-401491P	20020806 <--
	Div ex	US 2003-634936	20030805
		US 2005-121862	20050504

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003251661	A1 Based on	WO 2004014907
EP 1539755	A1 Based on	WO 2004014907
BR 2003013297	A Based on	WO 2004014907

PRIORITY APPLN. INFO: **US 2002-401491P**
 20020806; US 2003-634936
 20030805; US 2005-121862

20050504

INT. PATENT CLASSIF.:

MAIN: A61K031-519; C07D471-02; C07D471-04

SECONDARY: A61P029-00; C07D487-02

BASIC ABSTRACT:

WO2004014907 A UPAB: 20040331

NOVELTY - 2,6-Disubstituted 7-oxo-pyrido(2,3-d)pyrimidines are new.

DETAILED DESCRIPTION - 2,6-Disubstituted 7-oxo-pyrido(2,3-d)pyrimidines of formula (I), their salts, hydrates or prodrugs are new.

Z = N or CH;

X1 = O, NR4, S or C(O);

R4 = H or alkyl;

R1 = T1, alkenylene or -CH2-alkenyl;

T1 = (cyclo)alkyl, cycloalkylalkyl;

R2 = H, T1, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, alkylene-C(O)-R21, amino, monoalkylamino, dialkylamino, acyl or NR22-Y-R23;

R21 = H, alkyl OH, alkoxy, amino, monoalkylamino or dialkylamino;

Y = -C(O), -C(O)O-, -C(O)NR24, S(O)2 or S(O)2NR25;

R22, R24 and R25 = H or alkyl;

R23 = H, T1, heteroalkyl or optionally substituted phenyl;

R3 = H, haloalkyl, (hetero)aryl, (hetero)aralkyl, T1, heteroalkyl substituted cycloalkyl, hetero-substituted cycloalkyl, heteroalkyl, cyanoalkyl, heterocyclyl, heterocyclylalkyl, or -heterocycloamino-SO2-R12; and

R12 = haloalkyl, (hetero)aryl, arylalkyl or heteroaralkyl.

INDEPENDENT CLAIMS are included for the following:

(1) preparation of (I); and

(2) use of (I) in the manufacture of medicament for the treatment of a p38 mediated disorder e.g. rheumatoid arthritis.

ACTIVITY - Antiarthritic; Antirheumatic; Antipsoriatic; Antiinflammatory; Gastrointestinal-Gen.; Respiratory-Gen.; Antiasthmatic; Neuroprotective; Nootropic; Immunosuppressive; Ophthalmological; Dermatological; Cardiovascular-Gen.; CNS-Gen.; Antidiabetic; Antipyretic; Antigout; Osteopathic; Virucide; Antibacterial; Antimalarial; Immunomodulator; Anti-HIV; Vasotropic; Antiartherosclerotic; Thrombolytic; Anticoagulant; Cardiant; Nephrotropic; Hepatotropic; Vulnerary; Antiulcer; Uropathic; Cytostatic; Antiangiogenic; Gynecological.

MECHANISM OF ACTION - p38-(Mitogen-activated protein kinases (MAP))kinase inhibitor; LPS-induced TNF- alpha -production inhibitor.

An in vitro assay of p38(MAP)kinase was evaluated as follows: p-38 MAP kinase inhibitory activity of hydrochloride of 6-ethoxy-8-methyl-2-(((1-methanesulfonyl)piperidinyl-4-yl)amino)pyrido(2,3-d)pyrimidin-7(8H)one (Ia) was determined by measuring the transfer of the gamma-phosphate from gamma -33P-ATP by p-38 kinase to Myelin Basic Protein (MBP) using minor modification of the method described in Ahn et al., J. Biol. Chemical, 266:4220-4227(1991). The phosphorylated p38 MAP kinase was diluted in kinase buffer (containing 3-(N-morpholino)propanesulfonic acid (20 mM), pH 7.2, beta -glycerol phosphate (25 mM), ethylene glycol-bis(beta -aminoethyl ether)-N,N,N',N'-tetraacetic acid (5 mM), sodium ortho-vandate (1 mM), dithiothreitol (1 mM), magnesium chloride (40 mM)). The test compound dissolved in dimethylsulfoxide (DMSO) or only DMSO (control) was added and the samples were incubated for 10 minutes at 30 deg. C. After incubation, for an additional 20 minutes at 30 deg. C, the reaction was terminated by adding phosphoric acid (0.75%) followed by separation of residual gamma -33P-ATP. The IC50 value of the test compound was found to be approx. 0.058 micro M.

USE - As active substances for the manufacture of medicament for the treatment of a p38 mediated disorder e.g. rheumatoid arthritis, ankylosing

spondylitis, psoriatic arthritis, Crohn's disease, irritable bowel syndrome, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, asthma or chronic obstructive pulmonary disease, Alzheimer's disease (all claimed). Also useful for the treatment or prophylaxis of inflammatory, immunological, oncological, bronchopulmonary, dermatological and cardiovascular disorders; in the treatment of central nervous system disorders or diabetic complications or for the prevention of graft rejection following transplant surgery; for the treatment of inflammation in a subject; as antipyretics for the treatment of fever, arthritis (including spondyloarthropathies), gouty arthritis, psoriatic arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, and other arthritic conditions; for the treatment of pulmonary disorders or lung inflammation (including adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, and chronic pulmonary inflammatory disease; for the treatment of viral and bacterial infections (including sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to or malignancy, cachexia secondary to AIDS, ARC (AIDS related complex), pneumonia, and herpes virus; for the treatment of bone resorption diseases (such as osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease (including graft versus host reaction and allograft rejections), cardiovascular diseases (including atherosclerosis, thrombosis, congestive heart failure, and cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection); for the treatment of Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus (SLE), skin-related conditions (such as psoriasis, eczema, burns, dermatitis, keloid formation, and scar tissue formation; for treating gastrointestinal conditions (such as gastritis and ulcerative colitis); in the treatment of **ophthalmic** disease (such as retinitis, retinopathies, uveitis, **ocular** photophobia, and of acute injury to the **eye** tissue); in treating angiogenesis (including neoplasia, metastasis; **ophthalmological** conditions (such as **corneal** graft rejection, **ocular** neovascularization, retinal neovascularization (including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas (including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone); diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis; for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, irritable bowel syndrome, inflammatory bowel disease, psoriasis, adult respiratory distress syndrome, asthma or chronic obstructive pulmonary disease or Alzheimer's disease or oncological disorders; for veterinary treatment of companion animals, exotic animals and farm animals (including mammals or rodents).

ADVANTAGE - (I) possess the desired pharmacological activity.

Dwg. 0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; GI; DCN
MANUAL CODES:	CPI: B06-D06; B06-D08; B14-A01; B14-A02; B14-A03B; B14-C03; B14-C04; B14-C06; B14-C09; B14-D07C; B14-E08; B14-E10B; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F04; B14-F05; B14-F07; B14-G01; B14-G02; B14-G03; B14-H01; B14-J01A4; B14-K01; B14-N01; B14-N03 ; B14-N10; B14-N12; B14-N14; B14-N16; B14-N17; B14-S01; B14-S04; B14-S06; B14-S12
TECH	UPTX: 20040331

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) involves: treating a compound formula (Ie) or its corresponding sulfoxide with R3-NH2.

Preferred Compound: 2,6-Disubstituted 7-oxo-pyrido(2,3-d)pyrimidines (I) is of formula (Ia) or its isomer, prodrug or salt (where X is -N(R12a)- and R12a is -S(O)2(1-4C alkyl)).

X = -O-, -C(O)-, -N(R12a)- or -CH(R12b)-;

R12a = H, 1-4C alkyl, -C(O)R15, -C(O)2R15 or -S(O)2(1-4C alkyl);

R12b = R12a or -OR15;

R14 = 1-4C alkyl, oxo, -OR15, -C(O)R15, -C(O)2R15 or -S(O)2(1-4C alkyl);

R15 = H or 1-4C alkyl;

q = 0 or 1;

r = 0 - 2.

ABEX

UPTX: 20040331

ADMINISTRATION - (I) is administered in a dosage of 0.1 - 100 (preferably 0.5 - 5) mg/kg orally, through nasal sprays, rectally (including suppositories) or parenterally (including by injection).

EXAMPLE - Crude 6-ethoxy-8-methyl-2-(((1-methanesulfonyl)piperidinyl-4-yl)amino)pyrido(2,3-d)pyrimidin-7(8H)one (0.92 g) was taken up in dichloromethane (DCM) (5 ml) with sodium carbonate (0.05 g) and methanesulfonyl chloride (0.022 ml) and stirred at room temperature (rt) for 17 hours. An additional aliquot of methane sulfonyl chloride (0.04 ml) and sodium carbonate (50 mg) were added and the reaction was stirred at rt for 24 hours. A final aliquot of methane sulfonyl chloride (0.080 ml) and sodium carbonate (150 mg) was added and reaction was stirred at rt for 48 hours. All starting materials were consumed and the organic layer was washed with water and dried with magnesium sulfate. After work up, 6-ethoxy-8-methyl-2-(((1-methanesulfonyl)piperidinyl-4-yl)amino)pyrido(2,3-d)pyrimidin-7(8H)one (Ia) was obtained.

DEFINITIONS - Preferred Definitions:

Z = N;

X1 = O;

R1 = ethyl;

R2 = methyl;

R3 = (1-hydroxy-2-methyl)-prop-2-yl, 1-hydroxy-pentan-2-yl, (S)-2-hydroxy-1,2-dimethyl-propyl, (R)-2-hydroxy-1,2-dimethyl-propyl, (S)-2-hydroxy-1-methyl-ethyl, 1-hydroxymethyl-cyclopentan-1-yl, 2-hydroxy-2-methyl-propyl, 3-methoxy-1(2-methoxy-ethyl)propyl, tetrahydro-2H-pyran-4-yl, 1-(methylsulfonyl)piperidin-4-yl, 1-(carboxyethyl)piperidin-4-yl, 1,1-dioxidotetrahydro-2H-thiopyran-4-yl, or morpholinyl.

L638 ANSWER 58 OF 94

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ACCESSION NUMBER: 2004-191124 [18] WPIX

CROSS REFERENCE: 2003-120349 [11]

DOC. NO. CPI: C2004-075355

TITLE: New substituted 2-amino nicotinamide derivatives useful in the treatment of cancer, angiogenesis and diabetic retinopathy.

DERWENT CLASS: B02 B03 B05

INVENTOR(S): ASKEW, B; BOOKER, S; CHEN, G; DIPIETRO, L V; ELBAUM, D; GERMAIN, J; HABGOOD, G J; HUANG, Q; KIM, T; LI, A; NISHIMURA, N; NOMAK, R; PATEL, V F; RIAHI, B; YUAN, C C; ASKEW, B C

PATENT ASSIGNEE(S): (AMGE-N) AMGEN INC

COUNTRY COUNT: 102

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
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WO 2004007481  A2 20040122 (200418)* EN 424 C07D401-12
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
    LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W:  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
    DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
    KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
    RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM
    ZW
AU 2003263784  A1 20040202 (200450)          C07D401-12
EP 1562933      A2 20050817 (200554)  EN      C07D401-12
R:  AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
    MC MK NL PT RO SE SI SK TR

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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004007481	A2	WO 2003-US22275	20030715
AU 2003263784	A1	AU 2003-263784	20030715
EP 1562933	A2	EP 2003-764755	20030715
		WO 2003-US22275	20030715

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003263784	A1 Based on	WO 2004007481
EP 1562933	A2 Based on	WO 2004007481

PRIORITY APPLN. INFO: **US 2002-197918**
20020717

INT. PATENT CLASSIF.:

MAIN: C07D401-12
SECONDARY: A61K031-4433; A61K031-4439; A61K031-444; C07D401-14;
C07D405-14; C07D407-14; C07D413-14; C07D417-14

BASIC ABSTRACT:

WO2004007481 A UPAB: 20050823
NOVELTY - Substituted 2-amino nicotinamide derivatives and their salts are new.

DETAILED DESCRIPTION - Substituted 2-amino nicotinamide derivatives of formula (I) and their salts are new.
R = 6-indazolyl, 1-oxo-2,3-dihydro-1H-isoindol-4-yl,
2-oxo-2,3-dihydro-1H-benzimidazol-5-yl or 4-oxo-3,4-dihydro-quinazolin-6-yl;

R1 = aryl, cycloalkyl, 5-6 membered heteroaryl, 9-10 membered bicyclic, 11-14 membered tricyclic heterocyclyl (all optionally substituted by at least one of 3-6C cycloalkyl, phenyl, phenyl-1-4C alkenyl, phenyloxy, 4-6 membered heterocyclyl-1-6C alkyl, 4-6 membered heterocyclyl-2-4C alkenyl, 4-6 membered heterocyclyl, 4-6 membered heterocycliloxy, 4-6 membered heterocyclyl-1-4C alkoxy, 4-6 membered heterocyclylsulfonyl, 4-6 membered heterocyclylamino, 4-6 membered heterocyclylcarbonyl, 4-6 membered heterocyclyl-1-4C alkylcarbonyl, 4-6 membered heterocyclylcarbonyl-1-4C alkyl, 4-6 membered heterocyclyl-1-4C alkylcarbonylamino, 4-6 membered heterocyclyl-oxycarbonylamino (all optionally substituted), halo, 1-6C alkyl, 1-2C haloalkoxy, 1-2C haloalkyl, 1-4C aminoalkyl, NO₂, NH₂, 1-3C alkylsulfonlamino, OH, CN, aminosulfonyl, 1-2C alkylsulfonyl, halosulfonyl, 1-4C alkylcarbonyl, amino-1-4C alkylcarbonyl, 1-3C alkylamino-1-4C alkylcarbonyl, 1-3C alkylamino-1-4C-alkylcarbonylamino, 1-4C alkoxycarbonyl-1-4C alkyl, 1-3C

alkylamino-1-3C alkyl, 1-3C alkylamino-1-3C alkoxy, 1-3C alkylamino-1-3C alkoxy-1-3C alkoxy, 1-4C alkoxycarbonyl, 1-4C alkoxycarbonylamino-1-4C alkyl, 1-3C alkylsulfonylamino-1-3C alkoxy, 1-4C hydroxyalkyl, 1-4C alkoxy or -C(Re)(Rf)OR₇;

Re and Rf = H or 1-2C haloalkyl; and

R₇ = phenyl, phenyl-1-3C alkyl, 4-6 membered heterocyclyl, 4-6 membered heterocyclyl-1-3C alkyl, 1-3C alkoxy-1-2C-alkyl, 1-3C alkoxy-1-3C alkoxy-1-3C alkyl (all optionally substituted), H or 1-3C alkyl.

INDEPENDENT CLAIMS are included for the following:

- (1) a composition (C1) comprising (I);
- (2) use of (I) for preparing a medicament useful in the treatment of e.g. cancer, angiogenesis-related diseases; and
- (3) treatment of cancer involving administration of (I).

ACTIVITY - Cytostatic; Antiangiogenic; **Ophthalmological**; Antidiabetic; Antiarthritic; Antirheumatic; Antipsoriatic; Antiinflammatory; Antiarteriosclerotic; Vulnerary; Antiulcer; Osteopathic; Antipyretic; Antithyroid; Cerebroprotective; Vasotropic; Antiallergic; Immunosuppressive; Gynecological; Antibacterial; Fungicide; Virucide; Anti-HIV; Protozoacide; Antiemetic; Dermatological; Antisickling; Cardiovascular-Gen.; Gastrointestinal-Gen.; Antianemic;

MECHANISM OF ACTION - Tumor growth inhibitor; Angiogenesis inhibitors; Vascular endothelial growth factor kinase inhibitor (VEGFR); Protein kinase p38 inhibitor; Epidermal growth factor receptor-associated protein kinase inhibitor (EGFR); Cyclin dependent kinase inhibitor-2 (CDK-2); Cyclin dependent kinase inhibitor-5 (CDK-5); Nuclear factor kappa B kinase inhibitor (IKK); c-Jun-N-terminal kinase inhibitor-3 (JNK3); Basic fibroblast growth factor receptor-associated protein kinase inhibitor (bFGFR); platelet derived growth factor receptor-associated protein kinase inhibitor (PDGFR); RAF kinase inhibitor; Tumor necrosis factor kinase inhibitor (TNF); Metallomatrix proteases inhibitor (MMP); Cyclooxygenase inhibitor-2 (COX-2).

Test details are described, but no specific result given.

USE - In the preparation of medicament for the treatment of cancer, angiogenesis-related diseases, neoplasia, **ophthalmological** conditions, diabetic retinopathy, KDR-related disorders, proliferation related disorders; for reducing blood flow in tumor, and reducing tumor size (claimed). Also useful in the treatment of metastasis, Kaposi's sarcoma, **corneal graft rejection**, **ocular** neovascularization, retinal neovascularization including neovascularization following injury or infection, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases e.g. gastric ulcer; pathological, non-malignant conditions such as hemangiomas (including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone); and disorders of the female reproductive system (including endometriosis), edema, vascular hyperpermeability, proliferative diseases, inflammatory rheumatoid or rheumatic disease (including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy), paraneoplastic syndrome or tumor-induced inflammatory diseases, systemic Lupus erythematosus, poly-myositis, dermato-myositis, systemic scleroderma or mixed collagenosis; seronegative spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; synovial inflammation (e.g. synovitis, including any of the particular forms of synovitis, in particular bursal synovitis and purulent synovitis), associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans, inflammatory diseases, of the joints, insertion endopathy, myofasciale syndrome and tendomyositis, dermatomyositis and myositis, arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb

angiogenesis, wound healing, peptic ulcer, Helicobacter related diseases, fractures, cat scratch fever, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, polycystic ovarian syndrome (Stein- Leventhal syndrome)) metastasis, burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, **ocular** and macular edema, ascites, disorders involving protein extravasation that leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome), ulcers (including bacterial, fungal, Mooren ulcers and ulcerative colitis), viral infections (including Herpes simplex, Herpes Zoster, AIDS), protozoan infections and toxoplasmosis, endometriosis, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma, obesity, **ocular** conditions (including **ocular** and macular edema, glaucoma, **ocular** neovascular disease, scleritis, radial **keratotomy**, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, **conjunctivitis**, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration), cardiovascular conditions (e.g. atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease).

ADVANTAGE - The compounds are potent vascular endothelial growth factor kinase inhibitors.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D01; B06-D02; B06-D03; B06-D05; B06-D07;
B06-D17; B14-A01; B14-A02; B14-A03; B14-A04;
B14-C03; B14-C04; B14-C06; B14-C09; B14-D06;
B14-E05; B14-E08; B14-E10; B14-F01; B14-F02;
B14-F02F2; B14-F03; B14-F07; B14-G02; B14-H01;
B14-N01; **B14-N03**; B14-N11; B14-N16;
B14-N17; B14-S04

TECH UPTX: 20040316

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) involves amidation of 2-chloronicotinic acid by an amine of formula R1NH2 followed by amination of the intermediate 2-chloro- nicotinamide derivative by an amine of formula R-NH2.

Preferred Composition: The composition additionally comprises antibiotic type agents, alkylating agents, anti-metabolite agents, hormonal agents, immunological agents or other neoplastic agents.

Preferred Method: The method further involves administration of antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents or miscellaneous agents.

ABEX UPTX: 20040316

WIDER DISCLOSURE - alpha-aminocarboxamide derivatives of formula (II).

A1 and A2 = C, CH or N;

A1+A2 = 5-6 membered partially saturated heterocyclyl, 5- or 6-membered heteroaryl, 9-, 10- or 11-membered fused partially saturated heterocyclyl, 9- or 10-membered fused heteroaryl, aryl or 4-, 5- or 6-membered cycloalkenyl;

X = -C(Z)N(R5a)R4-;

Z = O or S;

R = 4-6 membered heterocyclyl, 9-14 membered bicyclic or tricyclicl (optionally substituted by at least one of 4-6 membered heterocyclyl,

phenyl (all optionally substituted), halo, OR3, SR3, SO2R3, CO2R3, CON(R3)2, COR3, N(R3)2, SO2N(R3)2, NR3C(O)OR3, NR3C(O)R3, NR3C(O)N(R3)2, cycloalkyl, NO2, oxo, alkylaminoalkoxyalkoxy, CN, alkylaminoalkoxy, lower alkyl (substituted by R2), lower alkenyl (substituted by R2), lower alkynyl (substituted by R2) or substituted aryl;
 R1 = 6-10 membered aryl, 4-6 membered heterocyclyl or 9-14 membered bicyclic or tricyclic heterocyclyl (all optionally substituted by cycloalkyl, 4-6 membered heterocyclyl, phenyl (all optionally substituted), halo, oxo, OR3, SR3, SO2R3, CO2R3, CON(R3)2, COR3, N(R3)2, NH(1-4C alkenylR14), SO2N(R3)2, NR3C(O)OR3, NR3C(O)R3, NR3C(O)N(R3)2, halosulfonyl, CN, NO2, alkylaminoalkoxyalkoxy, alkylaminoalkoxy, lower alkyl (substituted by R2), lower alkenyl (substituted by R2) or lower alkynyl (substituted by R2));
 R2 = phenylalkyl, 4-6 membered heterocyclyl, heteroarylalkyl, phenyl (all optionally substituted), H, halo, oxo, OR3, SR3, CO2R3, CON(R3)2, COR3, N(R3)2, SO2N(R3)2, NR3C(O)OR3, NR3C(O)R3, NR3C(O)N(R3)2, haloalkyl, cycloalkyl, lower alkyl, CN, lower hydroxyalkyl, lower carboxyalkyl, NO2, lower alkenyl, lower alkynyl, 1-4C alkoxy-1-4C alkoxy, 1-4C alkoxy-1-4C alkoxy-1-4C alkoxy, lower (alkyl)aminoalkyl, lower haloalkyl;
 R3 = phenyl, 3-6 membered heterocyclyl, 3-6C cycloalkyl, 3-6C cycloalkylalkyl (all optionally substituted), H or lower (halo)alkyl;
 R4 = 2-4C alkylenyl, 2-4C alkenylenyl, 2-4C alkynylenyl (optionally one of the CH2 group replaced by O or -NH-), bond or OH;
 R5 = phenyl, lower aralkyl (both optionally substituted), H or lower alkyl;
 R5a = Phenyl (optionally substituted), H or lower alkyl; and
 R14 = phenyl, 4-6 membered heterocyclyl, 3-6C cycloalkyl (all optionally substituted) or H.

SPECIFIC COMPOUNDS - 79 Compounds are specifically claimed as (I) e.g. N-(4-chlorophenyl)(2-(1H-indazol-6-ylamino)(3-pyridyl))carboxamide (Ia).

ADMINISTRATION - Dosage is 0.01-500 (preferably 0.1-20) mg/kg. Administration is by oral, mucosal, topical, rectal, pulmonary, parental (including intravascular, intravenous, intraperitoneal, subcutaneous, intramuscular, intrasternal and by infusion).

EXAMPLE - A mixture of 2-chloronicotinic acid (4 g), 4-chloroaniline (3.2 g) and diisopropylethylamine (6 ml) in dichloromethane was added to 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide and 1-hydroxybenzotriazol. The mixture was stirred at room temperature overnight. (2-Chloro(3-pyridyl))-N-(4-chlorophenyl)carboxamide (Iaa) was obtained after basic work-up. Mixture of (Iaa) (260 mg) and 6-aminoindazole (150 mg) was heated at 150 degreesC for 2 hours to give N-(4-chlorophenyl)(2-(1H-indazol-6-ylamino)(3-pyridyl))carboxamide.

DEFINITIONS - Preferred Definitions:

R = 6-indazolyl, 1-oxo-2,3-dihydro-1H-isoindol-4-yl, 2-oxo-2,3-dihydro-1H-benzoimidazole or 4-oxo-3,4-dihydro-quinazolin-6-yl; and R1 = 3,3-dimethyl-2,3-dihydro-1H-indolyl (optionally substituted by pyrrolidin-1-ylcarbonyl, methylcarbonyl or methylsulfonyl) or 4,4-dimethyl-1,2,3,4-tetrahydro-1H-isoquinolinyl.

L638 ANSWER 59 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-191112 [18] WPIX
 CROSS REFERENCE: 2002-732685 [79]
 DOC. NO. CPI: C2004-075343
 TITLE: New 2-benzylaminonicotinamide derivatives used for treating cancer, angiogenesis and diabetic retinopathy.
 DERWENT CLASS: B02 B03

INVENTOR(S) : ASKEW, B; BOOKER, S; ELBAUM, D; GERMAIN, J; HABGOOD, G;
HANDLEY, M; KIM, J L; KIM, T; LI, A; NISHIMURA, N; PATEL,
V F; YUAN, C C
PATENT ASSIGNEE(S) : (AMGE-N) AMGEN INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004007457	A2	20040122	(200418)*	EN	325	C07D213-81	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW							
AU 2003256577	A1	20040202	(200450)			C07D213-81	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004007457	A2	WO 2003-US22276	20030715
AU 2003256577	A1	AU 2003-256577	20030715

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003256577	A1 Based on	WO 2004007457

PRIORITY APPLN. INFO: **US 2002-197960**
20020717

INT. PATENT CLASSIF.:

MAIN: C07D213-81
SECONDARY: A61K031-44; A61K031-4427; A61K031-4545; A61P035-00;
C07D401-12; C07D401-14; C07D407-12; C07D409-12;
C07D413-12; C07D417-12

BASIC ABSTRACT:

WO2004007457 A UPAB: 20040805

NOVELTY - 2-Benzylamino nicotinamide derivatives (I) are new.

DETAILED DESCRIPTION - 2-Benzylamino nicotinamide derivatives of formula (I) and their isomers are new.

R2 = phenyl (optionally substituted by at least one 3-6C cycloalkyl, phenyl, phenyl-1-4C alkylenyl, phenyloxy, 4-6 membered heterocyclyl-1-6C alkyl, 4-6 membered heterocyclyl-2-4C alkenyl, 4-6 membered heterocyclyl, 4-6 membered heterocyclyloxy, 4-6 membered heterocyclyl-1-4C alkoxy, 4-6 membered heterocyclylsulfonyl, 4-6 membered heterocyclylamino, 4-6 membered heterocyclylcarbonyl, 4-6 membered heterocyclyl-1-4C alkylcarbonyl, 4-6 membered heterocyclyl-1-4C alkylcarbonylamino or 4-6 membered heterocyclyloxycarbonylamino (all optionally substituted), halo, 1-6C alkyl, 1-2C haloalkoxy, 1-2C haloalkyl, 1-4C aminoalkyl, NO₂, NH₂, 1-3C alkylsulfonylamino, OH, CN, aminosulfonyl, 1-2C alkylsulfonyl, halosulfonyl, 1-4C alkylcarbonyl, amino-1-4C alkylcarbonyl, 1-3C alkylamino-1-4C alkylcarbonyl, 1-3C alkylamino-1-4C alkylcarbonylamino, 1-4C alkoxycarbonyl-1-4C alkyl, 1-3C alkylamino-1-3C alkyl, 1-3C alkylamino-1-3C alkoxy, 1-3C alkylamino-1-3C alkoxy-1-3C alkoxy, 1-4C alkoxycarbonyl, 1-4C alkoxycarbonylamino-1-4C alkyl, 1-3C alkylsulfonylamino-1-3C alkoxy, 1-4C hydroxyalkyl, C(Re)(Rf)ORg or 1-4C

alkoxy) or 9-10 membered tricyclic unsaturated or partially unsaturated heterocyclyl;

Re, Rf = H or 1-2C haloalkyl;

Rg = phenyl-1-3C alkyl or 4-6 membered heterocyclyl-1-3C alkyl (both optionally substituted), H, 1-3C alkyl, 4-6 membered heterocyclyl, 1-3C alkoxy-1-2C alkyl or 1-3C alkoxy-1-3C alkoxy-1-3C alkyl, and

R8 = at least one of phenyl, heterocyclyl, heterocyclyl-1-6C alkoxy, heterocyclyl-1-6C alkylamino, heterocyclyl-1-6C alkyl or heterocyclyl-2-4C alkynyl (all optionally substituted), halo, NH₂, NO₂, OH, 1-6C alkyl, 1-6C haloalkyl, 1-6C alkoxy, 1-6C haloalkoxy, 1-6C aminoalkyl, 1-6C hydroxyalkyl, aminosulfonyl, 3-6C cycloalkyl, 1-6C alkylamino, 1-6C alkylamino-1-6C alkyl, 1-6C alkylamino-2-4C alkynyl, 1-6C alkylamino-1-6C alkoxy or 1-6C alkylamino-1-6C alkoxy-1-6C alkoxy,

provided that when R8 is 4-hydroxy or 3-hydroxy, then R2 is not 3-trifluorophenyl.

An INDEPENDENT CLAIM is also included for a composition (C1) comprising (I).

ACTIVITY - Cytostatic; Antiangiogenic; **Ophthalmological**; Antidiabetic; Antiarthritic; Antirheumatic; Antipsoriatic; Antiinflammatory; Antiarteriosclerotic; Vulnerary; Antiulcer; Osteopathic; Antipyretic; Antithyroid; Cerebroprotective; Vasotropic; Antiallergic; Immunosuppressive; Gynecological; Antibacterial; Fungicide; Virucide; Anti-HIV; Protozoacide; Antiemetic; Dermatological; Antianemic; Antisickling; Cardiovascular-Gen.; Gastrointestinal-Gen.

MECHANISM OF ACTION - Vascular endothelial growth factor kinase inhibitor (VEGFR); Protein kinase p38 inhibitor; Epidermal growth factor receptor-associated protein kinase inhibitor (EGFR); Cyclin dependent kinase inhibitor-2 (CDK-2); Cyclin dependent kinase inhibitor-5 (CDK-5); Nuclear factor kappa B kinase inhibitor (IKK); c-Jun -N-terminal kinase inhibitor-3 (JNK3); Basic fibroblast growth factor receptor-associated protein kinase inhibitor (bFGFR); Platelet derived growth factor receptor-associated protein kinase inhibitor (PDGFR); Raf kinase inhibitor.

Tests are described, but no results given.

USE - Used for treating cancer, angiogenesis related diseases, neoplasia, **ophthalmological** conditions, KDR-related disorders, cell proliferation, reducing blood flow in tumor, reducing tumor size and diabetic retinopathy (claimed). (I) Are also used for treating metastasis, carcinoma, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, tumors of mesenchymal origin, tumors of the central and peripheral nervous system and other tumors, neoplasia, **ophthalmological** conditions, retrolental fibroplasia, neovascular glaucoma, retinal ischemia, vitreous hemorrhage, ulcerative diseases, pathological, non-malignant, conditions such as hemangiomas, disorders of the female reproductive system such as endometriosis, edema, vascular hyperpermeability, proliferative diseases, an inflammatory rheumatoid or rheumatic disease, especially of manifestations at the locomotor apparatus, such as inflammatory rheumatoid diseases, paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid effusions, collagenosis, such as systemic lupus erythematosus, polymyositis, dermatomyositis, systemic scleroderma or mixed collagenosis, postinfectious arthritis, seronegative spondylarthritis, vasculitis, sarcoidosis, arthrosis, synovial inflammation associated with disease, inflammatory diseases of the joints, insertion endopathy, myofasciale syndrome and tendomyositis, dermatomyositis and myositis, arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies, solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as

thyroid hyperplasia, cysts metastasis, burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced cerebral or pulmonary edema, **ocular** and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease, treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation, ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis, viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anaemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease, obesity, **ocular** conditions such as **ocular** and macular edema, glaucoma, **ocular** neovascular disease, scleritis, radial **keratotomy**, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, **conjunctivitis**, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration, for treating cardiovascular conditions such as atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

ADVANTAGE - (I) Minimize deleterious effects of VEGF.

Dwg. 0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-H; B07-H; B14-C03; B14-C04; B14-C06; B14-C09;
 B14-D06; B14-E08; B14-F01; B14-F02F2; B14-F07;
 B14-G02B; B14-H01B; B14-K01; B14-L06; B14-N01;
B14-N03; B14-N04; B14-N14; B14-N17; B14-S04

TECH UPTX: 20040316

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises reacting a nicotinamide compound of formula (II) with a benzaldehyde compound of formula (III) in the presence of NaBH(OAc)3.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition:

ABEX UPTX: 20040316

WIDER DISCLOSURE - Also stated to be new are alpha-aminocarboxamide derivatives of formula (II).

A1, A2 = C or N, or

A1 + A2 = 5- or 6-membered heteroaryl;

X = C(=Z)-N(R5), C(=Z)-N(R5)R4, C(O)-N(R5) or C(O)N(R5)R4;

Y = N(R5)C(Ra)(Rb), N(R5)C(Ra)(Rb)-Rc or N=CH;

Ra, Rb = H, halo, 1-4C alkyl (substituted by R1), or

Ra + Rb = 3-4C cycloalkyl;

Rc = 1-4C alkylenyl (where one of the CH2 is optionally substituted by O or NH);

Z = O or S;

R1 = phenylalkenyl (optionally substituted), T, H, oxo, lower alkyl, CN, lower hydroxyalkyl, lower carboxyalkyl, NO2, lower alkenyl, lower alkynyl, lower aminoalkyl, lower alkylaminoalkyl or lower haloalkyl;

T = 5- or 6-membered heterocyclyl, heteroarylalkylenyl or phenyl (all optionally substituted), halo, OR7, SR7, CO2R7, COR7, CON(R7)2, N(R7)2, SO2N(R7)2, NR7C(O)OR7, NR7C(O)R7 or cycloalkyl;

R2 = 6-10 membered aryl, 5- or 6-membered heterocyclyl or 9-11 membered heterocyclyl (all optionally substituted by cycloalkyl, 5- or 6-membered heterocyclyl or phenyl (all optionally substituted), halo, OR7, SR7,

SO₂R₇, CO₂R₇, COR₇, CON(R₇)₂, N(R₇)₂, SO₂N(R₇)₂, NR₇C(O)OR₇, NR₇C(O)R₇, NH(1-4C alkylenylR₇), lower alkyl substituted by R₁, CN, NO₂, lower alkenyl or lower alkynyl), cycloalkyl or cycloalkenyl;
 R₃ = aryl (substituted by T or lower alkyl optionally substituted by R₁, CN, NO₂, lower alkenyl or lower alkynyl);
 R₄ = 2-4C alkenyl, 2-4C alkenylenyl or 2-4C alkynylenyl (in which one CH₂ is optionally substituted by O or NH);
 R₅ = H, lower alkyl, phenyl or lower aralkyl;
 R₆ = H or 1-6C alkyl, and
 R₇ = H, lower alkyl, phenyl, 5- or 6-membered heterocyclyl, 3-6C cycloalkyl or lower haloalkyl.

SPECIFIC COMPOUNDS - 15 Compounds (I) are specifically claimed e.g:
 N-(4-sec-butylphenyl)-2-((4-fluorobenzyl)amino)nicotinamide (Ia).

ADMINISTRATION - Dosage is 0.01-500 (preferably 0.1-50) mg/kg.
 Administration is oral, mucosal, topical, rectal, pulmonary, parental (including intravascular, intravenous, intraperitoneal, subcutaneous, intramuscular, intrasternal and by infusion).
 Administration is optionally in combination with antibiotic type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon type agents or miscellaneous agents.

EXAMPLE - 2-Chloropyridin-3-carbonyl chloride (9.15 g) was added to a solution of 4-sec-butylaniline (10 g) and N,N-diisopropylethylamine (10 ml) in dichloromethane at room temperature and the mixture was stirred for 48 hours. After basic work-up 2-chloro-N-(4-sec-butylphenyl)-nicotinamide (Iaa) obtained as a white solid. (Iaa) (0.025 g) was aminated using 4-fluorobenzylamine (0.029 g) at 120degreesC neat for 18 hours to give N-(4-sec-butylphenyl)-2-((4-fluorobenzyl)amino)nicotinamide.

L638 ANSWER 60 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-399250 [37] WPIX
 DOC. NO. CPI: C2004-149456
 TITLE: New diazinopyrimidine derivatives are protein kinase inhibitors, useful for treating e.g. arthritis and inflammatory bowel disease.
 DERWENT CLASS: B02
 INVENTOR(S): CHEN, J J; LUK, K T; LUK, K
 PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (CHEN-I) CHEN J J; (LUKK-I) LUK K T; (HOFF) HOFFMANN LA ROCHE INC; (ROCH-N) ROCHE PALO ALTO LLC
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2004097493	A1	20040520	(200437)*		39	A61K031-549	
WO 2004046152	A1	20040603	(200437)	EN		C07D498-04	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP							
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG							
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC							
VN YU ZA ZM ZW							
AU 2003283393	A1	20040615	(200470)			C07D498-04	
EP 1565475	A1	20050824	(200556)	EN		C07D498-04	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							

US 6943158

B2 20050913 (200560)

C07D487-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
US 2004097493	A1 Provisional	US 2002-427652P	20021118	<--
		US 2003-715666	20031118	
WO 2004046152	A1	WO 2003-EP12652	20031112	
AU 2003283393	A1	AU 2003-283393	20031112	
EP 1565475	A1	EP 2003-775346	20031112	
		WO 2003-EP12652	20031112	
US 6943158	B2 Provisional	US 2002-427652P	20021118	<--
		US 2003-715666	20031118	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003283393	A1 Based on	WO 2004046152
EP 1565475	A1 Based on	WO 2004046152

PRIORITY APPLN. INFO: **US 2002-427652P**
20021118; US 2003-715666
20031118

INT. PATENT CLASSIF.:

MAIN: A61K031-549; C07D487-04; C07D498-04
SECONDARY: A61K031-519; A61K031-53; A61K031-5365; A61K031-5395;
A61P009-10; A61P011-00; A61P019-02; A61P025-28;
A61P029-00; A61P035-00; C07D487-02; C07D491-02;
C07D498-02; C07D513-04

BASIC ABSTRACT:

US2004097493 A UPAB: 20040611

NOVELTY - Diazinopyrimidine derivatives (I) are new.

DETAILED DESCRIPTION - Diazinopyrimidine derivatives of formula (I), or their salts are new.

R1, R5 and R6 = H or alkyl;

R2 = (halo)alkyl, (hetero)aryl, (hetero)aralkyl, (cycloalkyl)alkyl, heteroalkyl substituted cycloalkyl, heterosubstituted cycloalkyl, heteroalkyl, cyanoalkyl, (heterocyclyl)alkyl or -Y1-C(O)-Y2-R11;

Y1 and Y2 = absent or alkylene;

R11 = T or haloalkyl;

T = H, alkyl, OH, alkoxy, amino, mono- or di-alkylamino;

R3 = H, (cyclo)alkyl, cycloalkylalkyl, heterosubstituted cycloalkyl, heterocyclyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, alkylene-C(O)-R4 or acyl;

R4 = T;

Ar1 = aryl;

X1 = O, NR5 or S;

X2 = bond, O, NR6, S or CH2.

INDEPENDENT CLAIMS are included for the following:

(a) preparation of (I); and

(b) a diazinopyrimidine derivative of formula (II).

n = 0 - 2;

R7 = alkyl.

ACTIVITY - Antiarthritic; Antiinflammatory; Gastrointestinal-Gen.; Respiratory-Gen.; Antiarteriosclerotic; Vasotropic; Cytostatic; Antirheumatic; Osteopathic; Dermatological; Immunosuppressive; Antiasthmatic; Antibacterial; Virucide; Antimalarial; Immunomodulator; Anti-HIV; CNS-Gen.; Cardiant; Thrombolytic; Nephrotropic; Neuroprotective;

Antidiabetic; Antipsoriatic; Vulnerary; Antiulcer;
Ophthalmological; Antiangiogenic; Gynecological.

MECHANISM OF ACTION - p38 **Mitogen**-activated protein (MAP) kinase inhibitor; Fibroblast growth factor receptor (FGFR) kinase inhibitor.

The p38 MAP kinase inhibitory activity of 2-methyl-4-(2-chlorophenyl)-6-(tetrahydropyranyl-4-amino)-4H-1,3,4-pyrimido(4,5-e)oxadiazone (Ia) in vitro was evaluated by measuring the transfer of the gamma -phosphate from gamma -33P-ATP by p-38 kinase to Myelin Basic Protein (MBP), using modified method as described in Ahn, N. G.; et al. J. Biol. Chemical Volume 266(7), 4220 - 4227, (1991). (Ia) Showed an IC50 value of 0.189 micro M.

USE - For treating p38 MAP kinase mediated disorder (e.g. arthritis, Crohn's disease, inflammatory bowel disease, adult respiratory distress syndrome and chronic obstructive pulmonary disease) and FGFR kinase mediated disorder (e.g. atherosclerosis, restenosis and cancer) (all claimed). Also useful for treating rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, pulmonary disorders or lung inflammation (e.g. pulmonary sarcoidosis, asthma, silicosis and chronic pulmonary inflammatory disease), viral and bacterial infections (e.g. sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia and herpes virus), bone resorption diseases (e.g. osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease (e.g. graft versus host reaction and allograft rejections), cardiovascular diseases (e.g. thrombosis, congestive heart failure and cardiac reperfusion injury), renal reperfusion injury, liver disease, nephritis and myalgias due to infection, influenza, multiple sclerosis, diabetes, systemic lupus erthrematosis (SLE), skin-related conditions (e.g. psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation), gastrointestinal conditions (e.g. gastritis, irritable bowel disease and ulcerative colitis), **ophthalmic** diseases (e.g. retinitis, retinopathies, uveitis, **ocular** photophobia and of acute injury to the **eye** tissue), angiogenesis (e.g. neoplasia), metastasis, **ophthalmological** conditions (e.g. **corneal** graft rejection, **ocular** neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma), ulcerative diseases (e.g. gastric ulcer), hemangiomas (e.g. infantile hemangiomas), angiofibroma of the nasopharynx and avascular necrosis of bone, diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system (e.g. endometriosis).

ADVANTAGE - The compounds are inhibitors of protein kinases, and exhibit effective activity against p38 MAP kinase and FGFR kinase.

Dwg.0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-E03; B06-F03; B14-A01; B14-A02; B14-A03B;
 B14-D06; B14-E10; B14-F01; B14-F02; B14-F02D;
 B14-F02F2; B14-F04; B14-F07; B14-G01; B14-G02;
 B14-G03; B14-H01; B14-J01B3; B14-K01; B14-K01A;
 B14-N01; B14-N03; B14-N10; B14-N17;
 B14-S04

TECH UPTX: 20040611

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): Preparation of (I) involves contacting (II) with an amine compound of formula NHR1R2.

ABEX UPTX: 20040611

SPECIFIC COMPOUNDS - 31 Compounds are specifically disclosed as (I), e.g. 2-methyl-4-(2-chlorophenyl)-6-(tetrahydropyranyl-4-amino)-4H-1,3,4-

pyrimido(4,5-e)oxadiazine (Ia).

ADMINISTRATION - (I) Is administered in a dosage of 0.1 - 100 (preferably 0.5 - 5) mg/kg, orally, nasally, rectally or parenterally.

EXAMPLE - To 2-methyl-4-(2-chlorophenyl)-6-(methylthio)-4H-1,3,4-pyrimido(4,5-e)oxadiazine (0.367 g) in tetrahydrofuran (THF) (12 ml) was added a solution of oxone (0.89 g) in water (12 ml) at 0 degrees C. The mixture was stirred at room temperature for 4 hours. Ethyl acetate (50 ml) and water (50 ml) were added, and after work-up 2-methyl-4-(2-chlorophenyl)-6-(methylsulfinyl)-4H-1,3,4-pyrimido(4,5-e)oxadiazine (A1) was obtained. A mixture of (A1) (400 mg) and 4-aminotetrahydropyran (350 mg) in N-methylpyrrolidone (NMP) (0.3 ml) was heated at 110 degrees C for 24 hours. Ethyl acetate (60 ml) and water (25 ml) were added, and after work-up 2-methyl-4-(2-chlorophenyl)-6-(tetrahydropyranyl-4-amino)-4H-1,3,4-pyrimido(4,5-e)oxadiazine (180 mg) was obtained.

DEFINITIONS - Preferred Definitions:

R1 = H;

X1 = O;

R2 = heterocyclylphenyl, alkylthiophenyl, alkylsulfinylphenyl, alkylsulfonylphenyl, (halo)phenyl, hydroxyphenyl, acylphenyl, cyanophenyl, alkoxy-carbonylphenyl, carboxamidophenyl, N-alkylcarboxamidophenyl, N,N-dialkylcarboxamidophenyl, alkylsulfonyloxyphenyl, carbamoylphenyl, N-alkylcarbamoylphenyl or N,N-dialkylcarbamoylphenyl;

R3 = alkyl, heterocyclyl, heterosubstituted cycloalkyl or heteroalkyl;

X2 = bond or CH2;

Ar1 = 2-halophenyl, 4-halophenyl, 2,4-dihalophenyl, 2,6-dihalophenyl, 2-alkylphenyl, 1-alkoxyphenyl, 2-alkoxyphenyl, 4-alkoxyphenyl, 3,5-dialkoxyphenyl, 2-halo-5-alkoxyphenyl or 2-dialkylamino-6-fluorophenyl.

L638 ANSWER 61 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-294257 [27] WPIX
 DOC. NO. CPI: C2004-112549
 TITLE: Treatment of **dry eye** and other disorders requiring wetting of **eye**, comprising administering cytokine synthesis inhibitor to mammal.
 DERWENT CLASS: B05
 INVENTOR(S): GAMACHE, D A
 PATENT ASSIGNEE(S): (ALCO-N) ALCON INC
 COUNTRY COUNT: 37
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2004058875	A1	20040325	(200427)*		6	A61K038-08	
WO 2004026406	A1	20040401	(200431)	EN		A61P027-02<--	
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR							
W: AU BR CA CN JP KR MX PL US ZA							
AU 2003278727	A1	20040408	(200462)			A61P027-02<--	
EP 1542768	A1	20050622	(200541)	EN		A61P027-02<--	
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR							
BR 2003014603	A	20050726	(200551)			A61P027-02<--	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

US 2004058875	A1 Provisional	US 2002-412463P	20020920	<--
		US 2003-650006	20030826	
WO 2004026406	A1	WO 2003-US26689	20030826	
AU 2003278727	A1	AU 2003-278727	20030826	
EP 1542768	A1	EP 2003-770254	20030826	
		WO 2003-US26689	20030826	
BR 2003014603	A	BR 2003-14603	20030826	
		WO 2003-US26689	20030826	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003278727	A1 Based on	WO 2004026406
EP 1542768	A1 Based on	WO 2004026406
BR 2003014603	A Based on	WO 2004026406

PRIORITY APPLN. INFO: **US 2002-412463P**
20020920; US 2003-650006
20030826

INT. PATENT CLASSIF.:

MAIN: A61K038-08; **A61P027-02**
 SECONDARY: A61K031-192; A61K031-416; A61K031-505; A61K031-506;
 A61K031-551; A61K031-616

BASIC ABSTRACT:

US2004058875 A UPAB: 20040426
 NOVELTY - **Dry eye** disorders are treated by administering a composition comprising carrier and cytokine synthesis inhibitor consisting of **mitogen-activated kinase** inhibitors, **c-jun** N-terminal **kinase** inhibitors, I-kappa kinase inhibitors, IL-1 beta synthesis inhibitors, TNF alpha synthesis inhibitors, Janus family tyrosine kinase inhibitors, signal and activators of transcription inhibitors, or retinoid X receptor ligands.

ACTIVITY - **Ophthalmological.**

MECHANISM OF ACTION - Cytokine synthesis inhibitor.

USE - For treatment of **dry eye** and other disorders requiring wetting of the **eye**, which are symptoms of **dry eye** associated with **refractive surgery** (claimed).

ADVANTAGE - The method eliminates or improves **dry eye** conditions.

Dwg.0/1

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B06-D03; B06-D07; B06-D18; B07-H; B10-C03; B10-C04C;
 B14-D06; B14-L06; **B14-N03**

TECH UPTX: 20040426

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compounds: The cytokine synthesis inhibitor is **mitogen-activated (MAP) kinase** inhibitor, **p38 kinase** inhibitor, **c-jun** N-terminal **kinase** inhibitor or activator protein-1 inhibitor, selected from 5-(2-amino-4-pyrimidinyl)-4-(4-fluorophenyl)-1-(4-piperidinyl)imidazole, anthra(1,9-cd)pyrazol-6(2H)-one, pralnacasan, (D)Arginyl-(D)Norleucyl-(D)Norleucyl-(D)Arginyl-(D)Norleucyl-(D)Norleucyl-Glycine-(D)Tyrosine-amide acetate salt, 2-chloro-N-(3,5-di(trifluoromethyl)phenyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide, triflusal, or bexarotene.

ABEX UPTX: 20040426

ADMINISTRATION - Dosage comprises 0.001 - 1% (w/w) cytokine synthesis inhibitor which is administered topically to the **eye** (claimed).

EXAMPLE - An eye drop formulation was prepared by dissolving (% w/w) boric acid (0.25), sodium chloride (0.75), disodium edetate (0.01), and polyquaternium-1 (0.001) in 90% of the batch quantity of purified water. The pH was adjusted to 7.4 +/- 0.1 with sodium hydroxide or hydrochloric acid. Cytokine synthesis inhibitor (0.001 - 1) was added, and purified water was added to 100%. The mixture was stirred for 5 minutes to homogenize and was filtered through a sterilizing filter membrane into a sterile recipient.

L638 ANSWER 62 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-053140 [05] WPIX
 DOC. NO. CPI: C2004-021297
 TITLE: New 2-substituted 5-oxazolyl indole compounds useful for treating e.g. inflammatory or immune disease, T-cell mediated hypersensitivity diseases.
 DERWENT CLASS: B02 C02
 INVENTOR(S): DHAR, T G M; IWANOWICZ, E J; WATTERSON, S H
 PATENT ASSIGNEE(S): (DHAR-I) DHAR T G M; (IWAN-I) IWANOWICZ E J; (WATT-I) WATTERSON S H; (BRIM) BRISTOL-MYERS SQUIBB CO
 COUNTRY COUNT: 103
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003099206	A2	20031204	(200405)*	EN	27	A61K000-00	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL							
PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU							
ZA ZM ZW							
US 2003232866	A1	20031218	(200406)			A61K031-422	
AU 2003239508	A1	20031212	(200443)			A61K000-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003099206	A2	WO 2003-US15740	20030520
US 2003232866	A1 Provisional	US 2002-382128P	20020521 <--
		US 2003-441849	20030520
AU 2003239508	A1	AU 2003-239508	20030520

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003239508	A1 Based on	WO 2003099206

PRIORITY APPLN. INFO: **US 2002-382128P**
 20020521; US 2003-441849
 20030520

INT. PATENT CLASSIF.:
 MAIN: A61K000-00; A61K031-422
 SECONDARY: C07D413-14

BASIC ABSTRACT:
 WO2003099206 A UPAB: 20040120
 NOVELTY - 2-substituted 5-oxazolyl indole compounds are new.
 DETAILED DESCRIPTION - 2-substituted 5-oxazolyl indole compounds of

formula (I), their salts, hydrates or prodrugs are new.

R1 and R2 = T1, halo, cyano, -C(=O)R6, -CO2R6, -S(=O)R7, -SO2R7, -SO3R7, -OR6, -SR6, -NR6R7, -C(=O)NR6R7, -NR6C(=O)R7, NR6CO2R7, -NR6SO2R7 or SO2NR6R7;

T1 = H, optionally substituted alkyl, cycloalkyl, (hetero)aryl or heterocyclo;

R1+R2 = optionally substituted fused (5-6C) carbocyclic ring or 5- or 6-membered heterocyclo ring;

R3 = optionally substituted alkyl, (halo)alkoxy or halo;

R4 and R5 = optionally substituted alkyl, halo, cyano or -OR9;

R6 = T1;

R7 = T1, -S(=O)R7, -SO2R7 or -SO3R7;

R9 = H, optionally substituted 1-6C alkyl, cycloalkyl, (hetero)aryl or heterocyclo;

m and n = 0 - 2.

Provided that:

(1) R1 and R2 are not both H; and

(2) R7 is not H when attached to a sulfonyl group in -S(=O)R7, -SO2R7 or -SO3R7.

INDEPENDENT CLAIMS are also included for

(1) a pharmaceutical composition comprising at least one of (I) it's salts, hydrates or prodrugs; optionally at least one additional therapeutic agent; and carrier, adjuvant or vehicle. The therapeutic agent is immunosuppressant, anti-cancer agent, anti-viral agent, anti-inflammatory agent, anti-fungal agent, antibiotic, anti-vascular hyperproliferation compound, potassium channel opener, calcium channel blocker, sodium hydrogen exchanger inhibitor, anti-arrhythmic agent, thrombin inhibitor, platelet aggregation inhibitor, or anti-platelet agent, fibrinogen antagonist, diuretic, anti-hypertensive agent, mineralocorticoid receptor antagonist, phosphodiesterase inhibitor, cholesterol/lipid lowering agent, anti-diabetic agent, angiogenesis modulator, anti-coagulant, anti-proliferative agent, anti-tumor agent, anti-infective agent and/or second inosine monophosphate dehydrogenase (IMPDH) inhibitor; and

(2) inhibition of IMPDH activity in a mammal involving administering the composition.

ACTIVITY - Antiinflammatory; Immunosuppressive; Dermatological; Antirheumatic; Antiarthritic; Antipsoriatic; Tranquilizer; Vulnerary; Virucide; Neuroprotective; Antidiabetic; Antiasthmatic; Gastrointestinal-Gen.; Antiulcer; Muscular-Gen.; Antiseborrheic; Respiratory-Gen.; **Ophthalmological**; Hepatotropic; Antithyroid; Thyromimetic; Vasotropic; Antianemic; Nephrotropic; Antipruritic; Auditory; Endocrine-Gen.; CNS-Gen.; Osteopathic; Antimigraine; Analgesic; Antipyretic; Antibacterial; Nootropic; Antiparkinsonian; Antituberculostatic; Antitubercular; Antiasthmatic; CNS-Gen.; Anti-HIV; Cerebroprotective; Cytostatic; Fungicide; Antiarteriosclerotic; Cardiant; Anabolic; Hypertensive.

MECHANISM OF ACTION - Inosine monophosphate dehydrogenase (IMPDH) inhibitor; IMPDH enzyme activity inhibitor; Angiogenesis stimulator. Test details are described but no results given.

USE - For the treatment of an inflammatory or immune disease in a mammal (claimed). Also useful for the treatment of disorders which are mediated by IMPDH or for inhibiting IMPDH activity; for treating diseases associated with chronic and acute inflammation and immune-modulation e.g. transplant rejection (e.g. kidney, liver, heart, lung, pancreas (e.g. islet cells), bone marrow, **cornea**, small bowel), skin allografts, skin homografts (such as burn treatment), heart valve xenografts, serum, sickness, graft versus host disease, rheumatoid arthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, multiple sclerosis, juvenile diabetes, asthma, inflammatory bowel disease

(such as Crohn's disease and ulcerative colitis), pyoderma gangrenum, lupus (systemic lupus erythematosus), myasthenia gravis, psoriasis, dermatitis, dermatomyositis, eczema, seborrhea, pulmonary inflammation, **eye** uveitis, hepatitis, Grave's disease, Hashimoto's thyroiditis, autoimmune thyroiditis, Behcet's or Sjorgen's syndrome (**dry eyes**/mouth), pernicious or immunohaemolytic anaemia, glomerulonephritis, scleroderma, morphea, lichen planus, vitiligo (depigmentation of the skin), alopecia areata, autoimmune alopecia, autoimmune hypopituitarism, Guillain-Barre syndrome, alveolitis, osteoarthritis, osteoporosis, acute pancreatitis, chronic pancreatitis, Sezary's syndrome, migraine, cluster headaches, fever, sepsis, Alzheimer's disease, Parkinson's disease, Creutzfeldt-Jacob disease, multiple sclerosis and tuberculosis; respiratory allergies and diseases including (acute respiratory distress syndrome, hay fever, allergic rhinitis and chronic obstructive pulmonary disease), inflammatory disorders of the central nervous system, including HIV encephalitis, cerebral malaria, meningitis and ataxia telangiectasis; pain, T-cell mediated hypersensitivity, contact dermatitis (including that due to poison ivy), urticaria, skin allergies, respiratory allergies and gluten-sensitive enteropathy (Celiac disease); fungal infections such as mycosis fungoides, and in the treatment of autoimmune or DNA or RNA viral replication disease, such herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), cytomegalovirus, Epstein-Barr, human immunodeficiency virus (HIV), Addison's disease (autoimmune disease of the adrenal glands), idiopathic adrenal insufficiency, autoimmune polyglandular disease, chronic active hepatitis or acute hepatitis infection (including hepatitis A, hepatitis B, and hepatitis C), autoimmune gastritis, autoimmune hemolytic anemia and autoimmune neutropenia; vascular disease (e.g. atherosclerosis, transplant atherosclerosis, peripheral vascular disease, inflammatory vascular disease, intermittent claudication, restenosis, stenosis, cerebrovascular stroke, transient ischemic attack, myocardial ischemia and myocardial infarction); cancer and tumor disorders; for treating and preventing bacterial infection; for treating veterinary disease such as veterinary viral infections (including feline immunodeficiency virus, bovine immunodeficiency virus and canine immunodeficiency virus).

ADVANTAGE - (I) provides increased effectiveness and bioavailability, with fewer side effects. (I) selectively and directly inhibit key enzymes having significant biological effects such as IMPDH. (I) acts in a synergistic fashion with the therapeutic agent, and allows increased efficacy and reduced doses of the agent, and thus minimizing potential hemorrhagic side effects.

Dwg.0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; GI; DCN
MANUAL CODES:	CPI: B01-B01; B10-C03; B14-A01; B14-A02; B14-A03B; B14-A04; B14-C03; B14-C04; B14-C09; B14-D05D; B14-E08; B14-E10; B14-F01B; B14-F01G; B14-F02; B14-F07; B14-G01; B14-G02; B14-G02A; B14-H01; B14-J01A3; B14-J01A4; B14-K01; B14-N03 ; B14-N04; B14-N05; B14-N10; B14-N11; B14-N12; B14-N16; B14-N17; B14-R02; B14-S01; B14-S04; B14-S06; C01-B01; C10-C03; C14-A01; C14-A02; C14-A03B; C14-A04; C14-C03; C14-C04; C14-C09; C14-D05D; C14-E08; C14-E10; C14-F01B; C14-F01E; C14-F01G; C14-F02; C14-F07; C14-G01; C14-G02; C14-G02A; C14-H01; C14-J01A3; C14-J01A4; C14-K01; C14-N03 ; C14-N04; C14-N05; C14-N10; C14-N11; C14-N12; C14-N16; C14-N17; C14-R02; C14-S01; C14-S04; C14-S06

TECH

UPTX: 20040120

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) (where R₂ is H; and m and n are 0) involves heating aniline of formula (Ia) with an appropriately-substituted acetylene of formula H-C triple bond CR₁ (Ib) in a basic solvent (preferably triethylamine (TEA)) optionally with a co-solvent (preferably dioxane or tetrahydrofuran (THF)) up to the boiling point of the solvent in the presence of a palladium catalyst (preferably dichlorobis(diphenylphosphine)palladium (II)) and copper iodide to obtain acetylene of formula (Ic), followed by subsequent heating of (Ic) in N-methylpyrrolidine in the presence of a base (preferably potassium tert-butoxide).

Preferred Components: The therapeutic agent is anti-inflammatory agent selected from aspirin, non-steroidal antiinflammatory drug, TNF-alpha inhibitor, TNF-alpha antagonist, prednisone, dexamethasone, cyclooxygenase inhibitor, second IMPDH inhibitor, ICAM-1 inhibitor, prostaglandin synthesis inhibitor, a p38 mitogen-activated protein kinase inhibitor, protein tyrosine kinase inhibitor, IKK inhibitor, Maxi-K (RTM) opener, NF-kB inhibitor and nuclear translocation inhibitor.

ABEX

UPTX: 20040120

ADMINISTRATION - (I) is administered in a dosage of 0.1 - 500 mg/kg of body weight in a single dose or in the form of individual divided doses (such as 1 - 5 times per day), orally, sublingually, buccally, parenterally (including subcutaneously, intracutaneously, intravenously, intramuscularly, intraarticularly, intraarterially, intrasynovially, intrasternally, intrathecally, intralesionally, by intracranial injection, intrasternal injection or by infusion), nasally, by inhalation spray, topically, rectally, sublingually or buccally.

EXAMPLE - To a oven-dried flask under a nitrogen atmosphere were sequentially added ethyl 2-(methylthio)acetate (3.4 ml) and dichloromethane (DCM) (150 ml). The mixture was cooled to -78degreesC and sulfuryl chloride (26.31 ml) was added for 3 minutes. The reaction was stirred at -78degreesC for 15 minutes. A mixture of proton-sponge (5.64 g) and 5-(4-amino-2-methoxyphenyl)oxazole (5 g) in DCM (100 ml), was added dropwise for 1 hour. The reaction mixture was stirred at -78degreesC for two hours and quenched by adding triethylamine (TEA) (3.7 ml). The reaction mixture was allowed to warmed to room temperature (RT), stirred for one hour, and partitioned between DCM and water (100 ml). After work up, 1,3-dichloro-6-methoxy-3-(methylthio)-5-(5-oxazolyl)-2H-indol-2-one (A1) was obtained. To (A1) (1.7 g) in ethanol (20 ml) was added Raney-nickel and the contents were refluxed for 60 hours. The reaction mixture was filtered over Celite while hot and the Celite pad was washed. The filtrate was concentrated under reduced pressure to yield a solid (A2) (0.7 g), which was used as such for the subsequent step without further purification. To a solution of phosphorous oxybromide (2.18 g) in chloroform (20 ml) was added dimethylformamide (0.7 ml) at 0degreesC over a five minutes period. This was followed by the addition of (A2) at (RT). The reaction mixture was stirred at (RT) over night and quenched by the slow addition of 1 N sodium hydroxide (20 ml). After work up, 2-bromo-6-methoxy-5-(5-oxazolyl)-1H-indole-3-carboxaldehyde (0.06 g; yield 5%) was obtained.

DEFINITIONS - Preferred Definitions:

R₁ = 3H-11ambdaasterisk4asterisk-benzo(b)thiophen-3-yl (substituted by (R₁₅)_q);

R₁₅ = alkenyl, halo, (halo)alkyl, (halo)alkoxy, cyano, nitro, amino, alkylamino, aminoalkyl, hydroxy, hydroxyalkyl or alkylthio;

q = 0 - 2;

R₂ = cyano; and

R3 = O(1-4C alkyl)O or OCF3.

L638 ANSWER 63 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-022606 [02] WPIX
 DOC. NO. NON-CPI: N2004-017529
 DOC. NO. CPI: C2004-007047
 TITLE: Diagnosing glaucoma in a patient comprises detecting an aberrant level or bioactivity of Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway.
 DERWENT CLASS: B04 D16 P31
 INVENTOR(S): CLARK, A F; MCNATT, L G; WANG, W
 PATENT ASSIGNEE(S): (ALCO-N) ALCON INC; (CLAR-I) CLARK A F; (MCNA-I) MCNATT L G; (WANG-I) WANG W
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003092475	A2	20031113	(200402)*	EN	36	A61B000-00	
RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							
AU 2003237143	A1	20031117	(200442)			A61B000-00	
US 2005164907	A1	20050728	(200550)			G01N033-53	
TW 2003007754	A	20031216	(200557)			C12Q001-68	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003092475	A2	WO 2003-US13558	20030430
AU 2003237143	A1	AU 2003-237143	20030430
US 2005164907	A1	WO 2003-US13558	20030430
		US 2004-512324	20041022
TW 2003007754	A	TW 2003-112115	20030502

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003237143	A1 Based on	WO 2003092475

PRIORITY APPLN. INFO: **US 2002-377724P**
20020503

INT. PATENT CLASSIF.:

MAIN: A61B000-00; C12Q001-68; G01N033-53
 SECONDARY: A61F009-00; A61K038-17; C12N015-00

BASIC ABSTRACT:

WO2003092475 A UPAB: 20040107

NOVELTY - Diagnosing glaucoma in a patient comprises detecting the level or bioactivity of Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway in the patient, and comparing them to level in a normal sample.

DETAILED DESCRIPTION - Diagnosing glaucoma in a patient comprises:
 (a) obtaining a sample from the patient;

(b) detecting the level or bioactivity of Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway; and

(c) comparing the level or bioactivity of Wnt/PCP pathway component, frizzled related protein gene product of the Wnt/PCP pathway, or FRP of the Wnt/PCP pathway with the level in a normal sample or a sample with the sequence of a wildtype Wnt/PCP pathway component, frizzled related protein gene product of the Wnt/PCP pathway, or FRP of the Wnt/PCP pathway.

An aberrant level or bioactivity of Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway is indicative of a glaucomatous state. The presence of a genetic lesion in the sequence of Wnt/PCP pathway component, frizzled related protein gene product of the Wnt/PCP pathway, or FRP of the Wnt/PCP pathway obtained from the sample as compared to the wildtype sequence indicates a glaucomatous state.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of identifying an agent potentially useful for treating glaucoma;

(2) a method for treating glaucoma in a patient by administering a composition comprising a compound that modulates the level or bioactivity of a Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway; and

(3) a composition for treating glaucoma comprising a compound that modulates the level or bioactivity of a Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - Wnt/PCP modulator.

USE - The method is useful for diagnosing or treating glaucoma.

Compounds, which modulate the level or bioactivity of a Wnt/PCP pathway component, a frizzled related protein gene product of the Wnt/PCP pathway, or an FRP of the Wnt/PCP pathway, are useful for treating glaucoma.

Dwg.0/0

FILE SEGMENT: CPI GMPI

FIELD AVAILABILITY: AB

MANUAL CODES: CPI: B04-E01; B04-E06; B04-E07; B04-N02; B12-K04A;
B12-K04E; B14-L01; B14-L06; B14-N03;
D05-H09

TECH UPTX: 20040107

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In diagnosing glaucoma, the patient sample comprises cells of the trabecular meshwork tissue or patient tears. The planar cell polarity bioactivity is measured by determining the actin cytoskeletal organization. The altered actin cytoskeletal organization is diagnostic of glaucoma. Identifying an agent potentially useful for treating glaucoma comprises:

(a) contacting a cell expressing Wnt/PCP pathway component with a candidate substance;

(b) detecting a level or bioactivity of the Wnt/PCP pathway component in the presence of the candidate substance; and

(c) comparing the level or bioactivity of the Wnt/PCP pathway component in the presence of the candidate substance with that in the absence of the candidate substance.

An increase in the level or bioactivity of the Wnt/PCP pathway component in the presence of the candidate substance as compared to the level or bioactivity detected in the absence of the candidate substance identifies the candidate substance as an agent potentially useful for treating glaucoma. Alternatively, the method comprises:

(a) admixing a composition comprising a Wnt/PCP pathway component polypeptide with a candidate substance;

(b) adding a composition comprising a Wnt/PCP pathway component binding

partner to the solution obtained in (a) under conditions allowing the binding of the Wnt/PCP pathway component polypeptide to the Wnt/PCP pathway component binding partner;
 (c) detecting the interaction of the Wnt/PCP pathway component polypeptide with the binding partner; and
 (d) comparing the interaction of the Wnt/PCP pathway component polypeptide and the binding partner in the presence of the candidate substance with that in the absence of the candidate substance.
 An increase or decrease in the interaction of the Wnt/PCP pathway component polypeptide with the binding partner in the presence of the candidate substance as compared to that in the absence of the candidate substance identifies the candidate as an agent potentially useful for treating glaucoma. The Wnt/PCP pathway component is selected from sFRP, Wnt, Fzd, Flamingo, Dsh, rhoA, Drok, Pax3, DAPPER1, DAAM2, and JNK. The Wnt/PCP pathway component is preferably sFRP or Fzd, and the binding partner is Wnt, where a decrease of the interaction of sFRP and Wnt in the presence of the candidate substance as compared to the interaction in the absence of the candidate substance identifies the candidate substance as potentially useful for treating glaucoma. In treating glaucoma in a patient, the compound is selected from a protein, a peptide, a peptidomimetic, a small molecule or a nucleic acid consisting of a gene, antisense, ribozyme and triplex nucleic acid.

ABEX

UPTX: 20040107

ADMINISTRATION - Administration can be topical or parenteral (e.g. intravenous, subcutaneous or intramuscular) injection. No dosage given.

EXAMPLE - No relevant example given.

L638 ANSWER 64 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-812532 [76] WPIX
 DOC. NO. CPI: C2003-225947
 TITLE: New imidazo fused compounds useful for treatment of e.g. arthritis, Crohn's disease and adult respiratory distress syndrome.
 DERWENT CLASS: B02
 INVENTOR(S): GOLDSTEIN, D M; HAWLEY, R C; LUI, A S; SJOGREN, E B
 PATENT ASSIGNEE(S): (GOLD-I) GOLDSTEIN D M; (HAWL-I) HAWLEY R C; (LUIA-I) LUI A S; (SJOG-I) SJOGREN E B; (HOFF) HOFFMANN LA ROCHE & CO AG F
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003082871	A1	20031009	(200376)*	EN	31	C07D471-14	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW							
US 2003232847	A1	20031218	(200401)			A61K031-519	
AU 2003215675	A1	20031013	(200435)			C07D471-14	
EP 1492790	A1	20050105	(200504)	EN		C07D471-14	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							
BR 2003008937	A	20050104	(200510)			C07D471-14	
KR 2004099384	A	20041126	(200523)			C07D471-14	
US 2005197352	A1	20050908	(200559)			A61K031-519	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003082871	A1	WO 2003-EP3178	20030327
US 2003232847	A1 Provisional	US 2002-369929P	20020403 <--
		US 2003-406364	20030403
AU 2003215675	A1	AU 2003-215675	20030327
EP 1492790	A1	EP 2003-745276	20030327
		WO 2003-EP3178	20030327
BR 2003008937	A	BR 2003-8937	20030327
		WO 2003-EP3178	20030327
KR 2004099384	A	KR 2004-715609	20041001
US 2005197352	A1 Provisional	US 2002-369929P	20020403 <--
	Div ex	US 2003-406364	20030403
		US 2005-122137	20050504

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003215675	A1 Based on	WO 2003082871
EP 1492790	A1 Based on	WO 2003082871
BR 2003008937	A Based on	WO 2003082871

PRIORITY APPLN. INFO: **US 2002-369929P**
20020403; US 2003-406364
 20030403; US 2005-122137
 20050504

INT. PATENT CLASSIF.:

MAIN: A61K031-519; C07D471-14
 SECONDARY: A61K031-4745; A61P011-00; A61P025-00; A61P029-00;
 C07D487-14
 INDEX: C07D487-14; C07D471-14; C07D239:00; C07D239:00;
 C07D235:00; C07D235:00; C07D221:00

BASIC ABSTRACT:

WO2003082871 A UPAB: 20031125
 NOVELTY - Imidazo fused compounds (I), their salts, esters or prodrugs, are new.
 DETAILED DESCRIPTION - Imidazo fused compounds of formula (I), their salts, esters or prodrugs, are new:
 Z = N or CH;
 Z1 = N, CH or C;
 R1, R' = H or alkyl;
 R2 = aralkyl, cycloalkyl, heterocyclyl or (hetero)aryl (all optionally substituted), hydroxyalkyl or (hetero)alkyl;
 A = absent, -O-, -S(O)n-, -CHR'-, -C(=O)- or -NR3-;
 n = 0 - 2;
 R3 = (hetero)aryl or cycloalkyl (both optionally substituted), H or alkyl;
 Y = cycloalkyl or (hetero)aryl (both optionally substituted), or (hetero)alkyl; and
 a = single or double bond.
 An INDEPENDENT CLAIM is also included for the preparation of (I).
 ACTIVITY - Antiarthritic; Anti-inflammatory; Nootropic; Neuroprotective; Gastrointestinal Gen.; Respiratory Gen.; Antipyretic; Antirheumatic; Antigout; Antiasthmatic; Virucide; Antibacterial; Immunosuppressive; Antimalarial; Immunomodulator; Anti-HIV; Osteopathic; Vasotropic; Cardiovascular Gen.; Antiarteriosclerotic; Thrombolytic; Cardiant; Nephrotropic; Hepatotropic; Cytostatic; Antidiabetic;

Dermatological; Antipsoriatic; Vulnerary; Antiulcer;
Ophthalmological; Antiangiogenic; Antimetastatic; Gynecological.

MECHANISM OF ACTION - p-38 (mitogen activated protein (MAP)) kinase inhibitor.

The p-38 MAP kinase inhibitory activity of 4-(4-(2-chloro-phenyl)-3,7,9,9b-tetraazacyclopenta(a)naphthalen-8-ylamino)-cyclohexanol (A) in vitro was determined by measuring the transfer of gamma -phosphate gamma 33P-adenosine triphosphate (ATP) by p-38 kinase to Myelin Basic Protein (MBP), using the a minor modification of the method described in Ahn, N. G.; et al. J. of Biol. Chemical Volume 266(7), 4220 - 4227, (1991). (A) showed IC50 of 0.01 micro M.

USE - For treating a p38 mediated disorder (e.g. arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease) (claimed), fever, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, and other arthritic conditions, pulmonary disorder or lung inflammation (including pulmonary sarcoidosis, asthma, silicosis and chronic pulmonary inflammatory disease), viral and bacterial infection (including sepsis, septic shock or gram negative sepsis), malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to AIDS, AIDS, ARC (AIDS related complex), pneumonia, and herpes virus, bone resorption diseases (e.g. osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft vs. host reaction and allograft rejections), cardiovascular diseases (e.g. atherosclerosis, thrombosis, congestive heart failure and cardiac reperfusion injury), renal reperfusion injury, liver disease and nephritis and myalgias due to infection, influenza, multiple sclerosis, cancer, diabetes, skin-related conditions (e.g. psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation), gastritis and ulcerative colitis, **ophthalmic** disorders (e.g. retinitis, retinopathies, **corneal** graft rejection, **ocular** neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia, neovascular glaucoma, uveitis, **ocular** photophobia and acute injury to **eye** tissue), angiogenesis (e.g. neoplasia), metastasis, ulcerative diseases (e.g. gastric ulcer), pathological conditions (e.g. hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone), diabetic nephropathy and cardiomyopathy, and disorders of the female reproductive system (e.g. endometriosis).

ADVANTAGE - (I) Are inhibitors of protein kinases and exhibit effective activity against p38 in vivo.

Dwg.0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; GI; DCN
MANUAL CODES:	CPI: B06-D17; B14-A01; B14-A02; B14-A03B; B14-C03; B14-C04; B14-C09A; B14-C09B; B14-D01; B14-E08; B14-E10B; B14-E10C; B14-E11; B14-F01; B14-F02; B14-F04; B14-F05; B14-F07; B14-G01B; B14-G02C; B14-G02D; B14-H01; B14-J01A4; B14-K01; B14-N01; B14-N03 ; B14-N10; B14-N12; B14-N14; B14-N16; B14-N17; B14-P02; B14-S01; B14-S04; B14-S06

TECH UPTX: 20031125

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (claimed): (I) Are prepared by:

- (1) process A:
 - (i) reacting aldehyde of formula (Ia) with a cyanide of formula CN-CH₂-A-Y to form an amine of formula (Ib);
 - (ii) treating (Ib) with a reagent (e.g. triethylamine, trialkylamine base, 1,4-diazabicyclo(2.2.2)octane or diisopropylethylamine) and

1,2-dichloroethylether to form tricyclic sulfide compound of formula (Ic);
 (iii) oxidizing (Ic) with a reagent (A1) (e.g. 3-chloroperbenzoic acid, hydrogen peroxide/formic acid, hydrogen peroxide/methyltrioxorhenium VII or OXONE (RTM)) to obtain a sulfoxide compound of formula (Id); and
 (iv) contacting (Id) with an amine of formula H₂N-R₁R₂; or

(2) process B:

(i) reacting bicyclic compound of formula (Ie) with a reagent (e.g. triphenylphosphine, diethylazodicarboxylate or N-(2-hydroxyethyl)-phthalimide) to obtain bicyclic phthalimide of formula (If);
 (ii) reacting (If) with a hydrazine to obtain an amine of formula (Ig);
 (iii) reacting (Ig) with trimethylaluminum to obtain a compound of formula (Ih);
 (iv) optionally oxidizing (Ih) with the reagent (A1) to obtain the corresponding sulfoxide; and
 (v) contacting the sulfoxide with an amine of formula H₂N-R₁R₂.

R_p = lower alkyl or benzyl.

ABEX

UPTX: 20031125

SPECIFIC COMPOUNDS - 11 Compounds (I) are specifically disclosed, e.g. 4-(4-(2-chloro-phenyl)-3,7,9,9b-tetraazacyclopenta(a)naphthalen-8-ylamino)-cyclohexanol (A).

ADMINISTRATION - A daily dosage of (I) is 0.1 - 100 (preferably 0.5 - 5) mg/kg, and administration is enteral (e.g. oral), nasal (e.g. nasal spray), rectal (e.g. in the form of suppositories), or parental (e.g. in the form of injection).

EXAMPLE - 1,2-Dichloroethyl ethyl ether (4 ml) was added to a mixture of 2-benzylsulfanyl-6-(2-chloro-phenyl)-pyrido(2,3-d)pyrimidin-7-ylamine (3 g), triethylamine (4.8 g), water (5 ml) and acetonitrile (50 ml) over a period of 6 hours until reaction was completed. The mixture was allowed to stand overnight at room temperature, diluted with water and extracted with ethyl acetate. After work up, 8-benzylsulfanyl-4-(2-chloro-phenyl)-3,7,9,9b-tetraaza-cyclopenta(a)naphthalene (a) (2 g, 63% yield) was obtained. A mixture of (a) (0.056 g) and trans-4-aminocyclohexanol (0.053 g) in 1-methyl-2-pyrrolidinone (NMP) (1 ml) was heated in a 205 degrees C sand-bath (heating mantle) for 14 hours. After work up, 4-(4-(2-chloro-phenyl)-3,7,9,9b-tetraazacyclopenta(a)naphthalen-8-ylamino)-cyclohexanol (A) (0.39 g) was obtained.

DEFINITIONS - Preferred Definitions:

R₂ = 4-hydroxycyclohexyl, 4-tetrahydropyranyl, 4-(N-methyl-sulfonyl-piperidinyl), cyclopentyl, 4-tetrahydro-1,1-dioxide-2H-thiopyranyl, isopropyl or 4-fluorobenzyl;

A = absent or -O-;

R₁ = H;

Z = N;

Z₁ = N or CH; and

Y = phenyl (optionally substituted with halo, hydroxy, amino, alkyl or heteroaryl).

L638 ANSWER 65 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-788298 [74] WPIX

DOC. NO. CPI: C2003-217710

TITLE: Oral formulation of the crystalline free-base form of pyrrolidine acetamide derivative (DPC 333) useful as tumor necrosis factor-alpha convertase inhibitor for the treatment of inflammatory diseases e.g. rheumatoid arthritis.

DERWENT CLASS: B02

INVENTOR(S): BENEDEK, I H; FOSSLER, M J

PATENT ASSIGNEE(S): (BENE-I) BENEDEK I H; (FOSS-I) FOSSLER M J; (BRIM)
BRISTOL-MYERS SQUIBB CO

COUNTRY COUNT: 103

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003082287	A1	20031009	(200374)*	EN	39	A61K031-47	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL							
PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU							
ZA ZM ZW							
US 2003232079	A1	20031218	(200401)			A61K031-4709	
AU 2003214231	A1	20031013	(200435)			A61K031-47	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003082287	A1	WO 2003-US8404	20030314
US 2003232079	A1 Provisional	US 2002-366944P	20020322 <--
	Provisional	US 2002-400198P	20020801 <--
		US 2003-389525	20030314
AU 2003214231	A1	AU 2003-214231	20030314

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003214231	A1 Based on	WO 2003082287

PRIORITY APPLN. INFO: US 2002-400198P

20020801; US
2002-366944P 20020322;
US 2003-389525 20030314

INT. PATENT CLASSIF.:

MAIN: A61K031-47; A61K031-4709
SECONDARY: A61K009-22

BASIC ABSTRACT:

WO2003082287 A UPAB: 20031117

NOVELTY - Oral dosage form of crystalline, free-base (1-(R))-3-amino-N-hydroxy-alpha-(2-methylpropyl)-3-(4-((2-methyl-4-quinolinyl)methoxy)phenyl)-2-oxo-1-pyrrolidineacetamide (DPC 333) (I) provides a mean terminal disposition half-life (T_{1/2}) of about 2-7 hours when administered as a single dose ranging from 15-530 mg.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for

(a) an oral dosage form of DPC 333 providing greater than proportional increase in mean area under the plasma concentration versus time curve from time zero to time infinity (AUC) when administered as a single dose greater than 225 mg; and

(b) an oral dosage form of DPC 333 providing a decreased AUC of about 23% and a decreased mean maximum plasma concentration (C_{max}) of about 40% when administered with food (as compared to when administered in a fasted state).

ACTIVITY - Antimicrobial; Anticoagulant; Ophthalmological; Hepatotropic; Antialcoholic; Antiallergic; Antiasthmatic; Anabolic; Eating-Disorders-Gen.; Antiarteriosclerotic; Immunosuppressive;

Antiinflammatory; Vasotropic; Immunomodulator; Cardiant; Nootropic; Antipyretic; Cytostatic; Antigout; Hemostatic; Anti-HIV; Antibacterial; Neuroprotective; Osteopathic; Antiarthritic; Dermatological; Antipsoriatic; Uropathic; Antirheumatic; Cerebroprotective; Antiulcer; Muscular; Respiratory; Endocrine; Antiemetic.

MECHANISM OF ACTION - Tumor necrosis factor-alpha convertase (TACE) inhibitor.

USE - (I) is useful in the manufacture of a medicament for treating a condition or disease mediated by matrix metalloproteinases (MMPs), TACE and/or aggrecanase i.e. acute infection, acute phase response, age-related macular degeneration, alcoholic liver disease, allergy, allergic asthma, anorexia, aneurism, aortic aneurism, asthma, atherosclerosis, atopic dermatitis, autoimmune disease, autoimmune hepatitis, Bechet's disease, cachexia, calcium pyrophosphate dihydrate deposition disease, cardiovascular effects, chronic fatigue syndrome, chronic obstruction pulmonary disease, coagulation, congestive heart failure, corneal ulceration, Crohn's disease, enteropathic arthropathy, Felty's syndrome, fever, fibromyalgia syndrome, fibrotic disease, gingivitis, glucocorticoid withdrawal syndrome, gout, graft versus host disease, hemorrhage, HIV infection, hyperoxic alveolar injury, infectious arthritis, inflammation and inflammatory diseases (particularly rheumatoid arthritis), intermittent hydrarthrosis, Lyme disease, meningitis, multiple sclerosis, myasthenia gravis, mycobacterial infection, neovascular glaucoma, osteoarthritis, pelvic inflammatory disease, periodontitis, polymyositis/dermatomyositis, post-ischemic reperfusion injury, post-radiation asthenia, psoriasis, psoriatic arthritis, pulmonary emphysema, pyoderma gangrenosum, relapsing polychondritis, Reiter's syndrome, rheumatic fever, sarcoidosis, scleroderma, sepsis syndrome, Still's disease, shock, Sjogren's syndrome, skin inflammatory diseases, solid tumor growth and tumor invasion by secondary metastases, spondylitis, stroke, systemic lupus erythematosus, ulcerative colitis, uveitis, vasculitis, and Wegener's granulomatosis. (I) can be used in combination with one or more additional antiinflammatory agents i.e. selective COX-2 inhibitors, interleukin-1 antagonists, dihydroorotate synthase inhibitors, p38 MAP (mitogen activated protein) kinase inhibitors, tumor necrosis factor (TNF)-alpha sequestration agents and methotrexate in the manufacture of a medicament for treating inflammatory disorders. (All claimed.)

ADVANTAGE - Single ascending doses of (I) are safe, tolerable and have enhanced pharmacokinetic characteristics that make them useful as inhibitors of TACE for the treatment of diseases characterized by TNF alpha overproduction. (I) is rapidly and well absorbed upon oral administration, and is well tolerated. The safety, tolerability, and pharmacokinetics of (I) were evaluated in a double-blind, placebo controlled, ascending single dose study in healthy male and female human subjects. The results showed that upon oral administration, DPC 333 is rapidly and well absorbed, with Tmax values of less than 1 hour post dose. A greater-than-proportional increase in exposure (AUC) was observed at the 345 and 530 mg doses. The effect of food on the safety, tolerability and pharmacokinetics of (I) was also examined in a randomized, open label, two period balanced crossover study in one cohort of male subjects. Each subject received a single oral dose (225 mg) of (I) on 2 occasions administered at least one week apart, one in the fasting state and once after a high-fat meal. The administration of (I) with food decreased both the AUC (about 23%) and Cmax (about 40%) as compared to the fasting state.

Dwg.0/2

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B06-D02; B07-D03; B14-A01; B14-A02; B14-A02B1;
 B14-C02; B14-C03; B14-C04; B14-C06; B14-C09;

B14-D01; B14-E05; B14-E08; B14-E10; B14-E11;
B14-E12; B14-F01; B14-F02; B14-F04; B14-F07;
B14-G02A; B14-G02D; B14-H01; B14-J01; B14-J01A4;
B14-J02; B14-J05; B14-K01; B14-K01A; **B14-N03**
; B14-N05; B14-N07; B14-N12; B14-N17; B14-S01

TECH UPTX: 20031117

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: When administered as a single dose of 15 mg, (I) provides a Cmax of about 88-180 nM, Tmax of about 0.5-1 hour or an AUC of about 255-430 nM-hour. When administered as a single dose of 25 mg, (I) provides a Cmax of about 170-435 nM, a Tmax of about 0.5-1 hour or an AUC of about 450-900 nM-hour. When administered as a single dose of 40 mg, (I) provides a Cmax of about 355 nM-655 microM, a Tmax of about 0.25-1 hour or an AUC of about 930-1425 nM-hour. When administered as a single dose of 80 mg, (I) provides a Cmax of about 965 nM-1870 microM, a Tmax of about 0.5-1 hour or an AUC of about 2245-4160 nM-hour. When administered as a single dose of 120 mg, (I) provides a Cmax of about 1535-2345 nM, a Tmax of about 0.5-1 hour or an AUC of about 3335-6210 nm-hour. When administered as a single dose of 225 mg, (I) provides a Cmax of about 2625 nM-3650 microM, a Tmax of about 0.5-1 hour or an AUC of about 6380-9400 nM-hour. When administered as a single dose of 345 mg, (I) provides a Cmax of about 6585 nM-15420 nM, a Tmax of about 0.25-1 hour or an AUC of about 18375-28820 nM-hour. When administered as a single dose of 530 mg, (I) provides a Cmax of about 9450-18072 nM, a Tmax of about 0.5-1 hour or an AUC of about 22040-39480 nM-hour.

ABEX UPTX: 20031117

ADMINISTRATION - (I) may be orally administered as formulations comprising DPC powder and stock solutions of wetting agent, simple syrup, distilled water and/or hydrochloric acid. The formulation must be administered within four hours of preparation and must be vigorously shaken for 30 seconds immediately prior to administration. Following administration, distilled water is added to the bottle or bottles, shaken gently for a few seconds and then administered immediately to the subject. This step is repeated twice so that the total volume administered is approximately 240 ml (dose plus distilled water rinses).

EXAMPLE - Hydrochloric acid (4.3 ml, 36% w/w) was added to distilled water to total volume of 50 ml and sonicated for 1 minute to give a stock solution. DPC 333 powder (225 mg) was placed in a bottle and hydrochloric acid stock solution (1 ml) was added and the bottle vortexed until the powder is completely dissolved. Distilled water (14 ml) was then added and the bottle shaken vigorously for a few minutes.

L638 ANSWER 66 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-697480 [66] WPIX
DOC. NO. CPI: C2003-191774
TITLE: New substituted pyridinone derivatives are p38
mitogen-activated protein (MAP) **kinase**
modulators, useful for the treatment of e.g. arthritis,
cancer and AIDS.
DERWENT CLASS: B03
INVENTOR(S): ALVIRA, E; BLEVIS-BAL, R M; BOEHM, T L; DEVADAS, B;
DEVRAJ, R; DURLEY, R C; HICKORY, B S; HITCHCOCK, J;
JEROME, K D; LIU, S; MADSEN, H M; MARRUFO, L D; MCGEE, K
F; NAING, W; OWEN, T; PROMO, M A; RUCKER, P V; SAMBANDAM,
A; SCOTT, I L; SELNESS, S R; SHIEH, H S; WALKER, J; XING,
L; SHIEN, H S; DURLEY, R; HICKORY, B; MADSEN, H; MARRUFO,
L; PROMO, M; SCOTT, I; SELNESS, S; MARRUTO, L D
PATENT ASSIGNEE(S): (ALVI-I) ALVIRA E; (BLEV-I) BLEVIS-BAL R M; (BOEH-I)
BOEHM T L; (DEVA-I) DEVADAS B; (DEVR-I) DEVRAJ R;

(DURL-I) DURLEY R C; (HICK-I) HICKORY B S; (HITC-I) HITCHCOCK J; (JERO-I) JEROME K D; (LIUS-I) LIU S; (MADS-I) MADSEN H M; (MARR-I) MARRUTO L D; (MCGE-I) MCGEE K F; (NAIN-I) NAING W; (OWEN-I) OWEN T; (PROM-I) PROMO M A; (RUCK-I) RUCKER P V; (SAMB-I) SAMBANDAM A; (SCOT-I) SCOTT I L; (SELN-I) SELNESS S R; (SHIE-I) SHIEH H S; (WALK-I) WALKER J; (XING-I) XING L; (PHAA) PHARMACIA CORP

COUNTRY COUNT:

103

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003068230	A1	20030821	(200366)*	EN	526	A61K031-4412	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA							
ZM ZW							
US 2004058964	A1	20040325	(200422)			C07D401-02	
AU 2003217433	A1	20030904	(200428)			A61K031-4412	
EP 1490064	A1	20041229	(200502)	EN		A61K031-4412	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							
BR 2003007631	A	20041221	(200509)			A61K031-4412	
KR 2004084914	A	20041006	(200512)			C07D401-06	
NO 2004003820	A	20041109	(200519)			C07D213-64	
IN 2004002150	P1	20050401	(200559)	EN		A61K031-4412	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003068230	A1	WO 2003-US4634	20030214
US 2004058964	A1 Provisional	US 2002-357029P	20020214 <--
	Provisional	US 2002-436915P	20021230 <--
		US 2003-367987	20030214
AU 2003217433	A1	AU 2003-217433	20030214
EP 1490064	A1	EP 2003-713478	20030214
		WO 2003-US4634	20030214
BR 2003007631	A	BR 2003-7631	20030214
		WO 2003-US4634	20030214
KR 2004084914	A	KR 2004-712622	20040813
NO 2004003820	A	WO 2003-US4634	20030214
		NO 2004-3820	20040913
IN 2004002150	P1	WO 2003-US4634	20030214
		IN 2004-DN2150	20040723

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003217433	A1 Based on	WO 2003068230
EP 1490064	A1 Based on	WO 2003068230
BR 2003007631	A Based on	WO 2003068230

PRIORITY APPLN. INFO: US 2002-436915P

20021230; US

2002-357029P

20020214;

US 2003-367987 20030214

INT. PATENT CLASSIF.:

MAIN: A61K031-4412; C07D213-64; C07D401-02; C07D401-06
 SECONDARY: A61P029-00; A61P029-000; C07D211-72; C07D211-84;
 C07D213-644; C07D213-69; C07D213-699; C07D213-70;
 C07D213-700; C07D213-74; C07D213-744; C07D213-75;
 C07D213-755; C07D213-79; C07D213-799; C07D213-84;
 C07D213-844; C07D213-85; C07D213-855; C07D215-22;
 C07D215-222; C07D401-04; C07D401-044; C07D401-066;
 C07D401-10; C07D401-100; C07D401-12; C07D401-122;
 C07D401-14; C07D401-144; C07D405-04; C07D405-044;
 C07D405-06; C07D405-066; C07D405-12; C07D405-122;
 C07D405-14; C07D405-144; C07D409-06; C07D409-066;
 C07D409-14; C07D409-144; C07D413-10; C07D413-100

BASIC ABSTRACT:

WO2003068230 A UPAB: 20031014

NOVELTY - Substituted pyridinone derivatives (I) are new.

DETAILED DESCRIPTION - Substituted pyridinone derivatives of formula (I) and their salts, are new.

R1 = e.g. arylalkoxy, arylalkyl or arylalkanoyl (all optionally substituted);

R2 = e.g. (hetero)aryl, (hetero)alkyl, NH₂, heterocycloalkyl (all optionally substituted), H, OH or halo;R3 = e.g. arylalkoxycarbonyl, aryloxycarbonyl, arylalkyl, arylalkoxy (all optionally substituted), H, halo or NH₂;

R4 = H or optionally substituted alkyl; and

R5 = e.g. aryl, arylalkyl, arylthioalkyl or alkyl (all optionally substituted).

Full definitions are given in the DEFINITIONS (Full Definitions) section.

An INDEPENDENT CLAIM is also included for treatment of tumor necrosis factor (TNF) mediated disorders, p38 kinase mediated disorders, inflammation and/or arthritis using substituted pyridinone derivatives of formula (I').

R'₄ = H or alkyl (optionally substituted by 1-2 G or 1-4C alkyl-C(O)NR₆R₇ (where the aryl from arylalkoxy, arylalkyl is optionally substituted by 1-5 halo, OH, alkoxy, alkyl, CO₂- 1-6C alkyl, CONR₆R₇, NR₆R₇, R₆R₇N-1-6C alkyl-, NO₂, haloalkyl or haloalkoxy).

ACTIVITY - Antirheumatic; Antiarthritic; Osteopathic; Dermatological; Immunosuppressive; Antiinflammatory; Analgesic; Antipyretic; Respiratory-Gen.; Antiasthmatic; Cardiovascular-Gen.; Antiarteriosclerotic; Cardiant; Thrombolytic; Anticoagulant; Vasotropic; Cerebroprotective; Tranquilizer; Vulnerary; Gastrointestinal-Gen.; Antiulcer; **Ophthalmological**; Virucide; Antidiabetic; Antipsoriatic; Antibacterial; Immunosuppressive; Protozoacide; Immunomodulator; Anti-HIV; Neuroprotective; Gynecological; Cytostatic; Nootropic; Antiparkinsonian; Anticonvulsant.

MECHANISM OF ACTION - P38 **Mitogen**-Activated Protein (MAP) Kinase Modulator.

In an assay to determine p38- alpha kinase induced phosphorylation of epidermal growth factor receptor peptide (EGFR) in the presence of ³³P-ATP, preferred compounds (I) inhibited p38 kinase with IC₅₀ values of 1-25 micro M. No specific data given.

USE - Compounds (I) are useful in the treatment or prevention of inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, neuroinflammation, pain, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, cardiovascular disease, arteriosclerosis, myocardial infarction,

thrombosis, congestive heart failure, cardiac reperfusion injury, cardiomyopathy, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, brain trauma, brain edema, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, **ophthalmic** diseases, retinitis, retinopathies, uveitis, **ocular** photophobia, acute injury to the **eye** tissue, **ophthalmological** conditions, **corneal** graft rejection, **ocular** neovascularization, retinal neovascularization, neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasias, neovascular glaucoma, diabetes, diabetic nephropathy, skin-related conditions, psoriasis, eczema, burns, dermatitis, keloid formation, scar tissue formation, angiogenic disorders, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, endotoxic shock, toxic shock syndrome, autoimmune disease, graft vs. host reaction, allograft rejections, bone resorption diseases, osteoporosis, multiple sclerosis, disorders of the female reproductive system, endometriosis, hemagionomas, infantile hemagionomas, angiofibroma of the nasopharynx, avascular necrosis of bone, benign and malignant tumors/neoplasia, cancer, colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body, leukemia, lymphoma, systemic lupus erythematosus (SLE), angiogenesis including neoplasia, metastasis, central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, canine B-cell lymphoma, peripheral, neuropathy, treatment of TNF-mediated disorders and p38 kinase-mediated disorders (claimed).

Dwg.0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B05-B01B; B06-H; B07-D04A; B07-D04B; B14-A01;
 B14-A02; B14-A03B; B14-C01; B14-C03; B14-C04;
 B14-C09; B14-D06; B14-E08; B14-E10C; B14-F01;
 B14-F01B; B14-F02; B14-F02D; B14-F02F2; B14-F04;
 B14-F05; B14-F06; B14-F07; B14-G01B; B14-G02C;
 B14-H01; B14-J01; B14-J01A3; B14-J01A4; B14-K01;
 B14-K01A; B14-N01; **B14-N03**; B14-N10;
 B14-N12; B14-N14; B14-N16; B14-N17; B14-P01B;
 B14-P02; B14-S01; B14-S04; B14-S06

TECH UPTX: 20031014

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: 25 Methods of preparing (I) are described e.g. reacting 4-nitro-pyridine N-oxide with a compound of formula R'-CH₂OH in presence of base, Ac₂O/K₂CO₃, tetrahydrofuran (THF), and silica to give (I; R₃-R₅ = H, R₁ = Cl or Br and R₂ = CH₂R).

R' = (hetero)aryl, NH₂ or alkyl.

ABEX UPTX: 20031014

SPECIFIC COMPOUNDS - 1208 Compounds (I) are specifically claimed, e.g. 3-chloro-4-((2,4-difluorobenzyl)oxy)-1-((1-(2-hydroxy-2-methylpropanoyl)-

2,3-dihydro-1H-indol-5-yl)methyl)-6-methylpyridin-2(1H)-one (Ia).

ADMINISTRATION - Administration of (I) is 0.01-100, preferably 0.5-30 mg/kg/day orally, topically, parenterally (percutaneously, subcutaneously, intravascularly, intravenously, intramuscularly, intrathecally or by infusion), by inhalation, rectally or suppository.

EXAMPLE - A solution of 3-chloro-4-(2,4-difluorobenzoyloxy)-6-methyl-1-(2,3-dihydro-1H-indol-5-yl)methyl)-1H-pyridin-2-one (200 mg), 1-chlorocarbonyl-1-methylethyl acetate (104.3

1), triethylamine (133

1) and tetrahydrofuran (THF; 4 ml) was stirred at 25 degrees C for 20 minutes. The reaction was completed by liquid chromatography/mass spectrometry (LC-MS). Sodium hydroxide (1.5 ml) and methanol (2 ml) was added and stirred for 20 minutes to give 3-chloro-4-((2,4-difluorobenzoyl)oxy)-1-((1-(2-hydroxy-2-methylpropanoyl)-2,3-dihydro-1H-indol-5-yl)methyl)-6-methylpyridin-2(1H)-one (240 mg, 99 % yield).

DEFINITIONS - Full Definitions:

R1 = arylalkoxy, arylalkyl, arylalkanoyl (all optionally aryl-substituted by 1-5 halo, 1-4C alkyl, 1-4C alkoxy, NO₂, CN, haloalkyl, haloalkoxy or CO₂R), alkyl, hydroxyalkyl, dihydroxyalkyl, alkanoyl, alkoxy, alkoxyalkyl (all optionally substituted by 1-3 halo, 1-4C alkoxy, 1-4C alkoxy carbonyl or 3-7C cycloalkyl), alkenyl, alkynyl, arylalkynyl, CN, aryl, alkanoyl, alkoxy, alkoxyalkyl, haloalkyl, haloalkoxy, carboxyl, H, halo, NO₂ or carboxaldehyde;

R2 = H, OH, halo, OSO₂-1-6C alkyl, OSO₂-aryl, arylalkoxy, aryloxy, arylthio, arylthioalkoxy, arylalkynyl, alkoxy, aryloxy-1-6C alkyl, alkyl, alkynyl, OC(O)NH(CH₂)_naryl, OC(O)N(alkyl)(CH₂)_naryl, alkoxyalkoxy, dialkylamino, alkoxy, (aryl)alkyl, (hetero)aryl, heteroarylalkyl, arylalkenyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkoxy, NR₈R₉, dialkylamino or CO₂R (all optionally substituted by 1-5 phenyl, -SO₂-phenyl (both optionally substituted by 1-3 halo or NO₂ or -OC(O)NR₆R₇), halo, -1-6C alkyl-N(R)-CO₂R₃₀, haloalkyl, heteroaryl, heteroarylalkyl, NR₆R₇, R₆R₇N-(1-6C alkyl)-, C(O)NR₆R₇, -1-4C alkyl-C(O)NR₆R₇, -1-4C alkyl-NRC(O)NR₁₆R₁₇, haloalkoxy, alkyl, CN, hydroxyalkyl, dihydroxyalkyl, alkoxy or alkoxy carbonyl);

n = 0-6;

R₁₆, R₁₇ = H or 1-6C alkyl;

NR₁₆R₁₇ = morpholinyl ring;

R₆, R₇ = H, alkyl, hydroxyalkyl, dihydroxyalkyl, alkoxy, alkanoyl, arylalkyl, arylalkoxy, alkoxy carbonyl, -SO₂-alkyl, OH, alkoxy, alkoxyalkyl, arylalkoxy carbonyl, -1-4C alkyl-CO₂-alkyl, heteroarylalkyl or arylalkanoyl (all optionally substituted by 1-3 halo, OH, SH, heterocycloalkyl, heterocycloalkylalkyl, 3-7C cycloalkyl, alkoxy, NH₂, NH(alkyl), N(alkyl)₂, -O-alkanoyl, alkyl, haloalkyl, carboxaldehyde or haloalkoxy); or

NR₆R₇ = morpholinyl, pyrrolidinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, piperidinyl, pyrrolidinyl or piperazinyl ring (optionally substituted by 1-2 alkoxy carbonyl, 1-4C alkyl, 1-4C alkoxy, OH, hydroxyalkyl, dihydroxyalkyl or halo);

R = H or R₃₀;

R₃₀ = 1-6C alkyl (optionally substituted by 1-2 OH, SH, halo, (monoalkyl)amino, dialkylamino or 3-6C cycloalkyl);

R₈ = H, alkyl, alkanoyl, arylalkyl and arylalkanoyl (all optionally substituted by 1-5 alkoxy, alkoxy carbonyl, halo or (halo)alkyl);

R₉ = H, alkanoyl, (aryl)alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, heteroaryl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, arylalkanoyl, -SO₂-phenyl or aryl (all optionally substituted by 1-2 alkoxy, alkoxy carbonyl, halo or (halo)alkyl);

R₃ = arylalkoxy carbonyl, aryloxy carbonyl, arylalkyl, -OC(O)NH(CH₂)_naryl, arylalkoxy, -OC(O)N(alkyl)(CH₂)_naryl, arylthioalkoxy (all optionally

substituted by 1-5 halo, (halo)alkyl, or (halo)alkoxy), aryloxy, arylthio, thioalkoxy, alkenyl, NR6R7, NR6R7-1-6C alkyl, alkyl, H, halo or alkoxy carbonyl;

R4 = H or alkyl (optionally substituted by 1-2 G, C(O)R6, heteroarylalkyl or C(O)NR6R7 (where (hetero)aryl is optionally substituted by 1-5 halo, OH, alkoxy, alkyl, CO2-1-6C alkyl, CONR6R7, NR6R7, R6R7N-1-6C alkyl-, NO2, haloalkyl or haloalkoxy);

G = CO2R, -CO2-1-6C alkyl, C(O)NR6R7, N(R30)C(O)NR16R17, N(R30)C(O)-1-6C alkoxy, NR6R7, arylalkoxy, arylalkyl, heteroaryl, hydroxyalkyl, dihydroxyalkyl, haloalkyl, R6R7N-(1-6C alkyl)-, NR6R7, alkoxy, carboxaldehyde, CO2R, alkoxyalkyl or alkoxyalkoxy);

R5 = alkoxyalkyl, alkoxy (both optionally substituted by trimethylsilyl), aryl, arylalkyl, arylthioalkyl, alkyl (optionally substituted by 1-3 arylalkoxy carbonyl, NR8R9, halo, C(O)NR8R9, alkoxy carbonyl, 3-7C cycloalkyl or alkanoyl), alkoxy, NH2, alkoxy carbonyl, hydroxyalkyl, dihydroxyalkyl, alkynyl, -SO2-alkyl, heterocycloalkylalkyl, cycloalkyl, cycloalkylalkyl, alkyl-S-aryl, -alkyl-SO2-aryl, heteroarylalkyl, heterocycloalkyl, heteroaryl, alkenyl (optionally substituted by alkoxy carbonyl) (all optionally substituted by 1-5 halo, alkoxy, (hydroxy)alkyl, dihydroxyalkyl, arylalkoxy, thioalkoxy, alkoxy carbonyl, arylalkoxy carbonyl, CO2R, CN, OH, amidinoxime, NR6R7, NR8R9, R6R7N-(1-6C alkyl)-, carboxaldehyde, SO2alkyl, SO2H, SO2NR6R7, alkanoyl (all optionally alkyl-substituted by OH, halo or alkoxy, C(O)NR6R7, -1-4C alkyl-C(O)NR6R7, amidino, haloalkyl, -1-4C alkyl-NR15C(O)NR16R17, -1-4C alkyl-NR15C(O)R18, -OCH2O-, -OCH2CH2O- or haloalkoxy) or H;

R15 = H or 1-6C alkyl; and

R18 = 1-6C alkyl (optionally substituted by -O-2-6C alkanoyl, 1-6C hydroxyalkyl, 1-6C dihydroxyalkyl, 1-6C alkoxy, 1-6C alkoxy 1-6C alkyl), amino-1-6C alkyl, mono- or dialkylamino-1-6C alkyl.

L638 ANSWER 67 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-608032 [57] WPIX
 DOC. NO. CPI: C2003-165755
 TITLE: Composition useful for treatment of e.g. pain and inflammation comprises a peroxisome proliferator activated receptor-alpha agonist and a cyclooxygenase-2 selective inhibitor.
 DERWENT CLASS: B05
 INVENTOR(S): OBUKOWICZ, M G
 PATENT ASSIGNEE(S): (PHAA) PHARMACIA CORP
 COUNTRY COUNT: 103
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003059294	A2	20030724	(200357)*	EN	78	A61K000-00	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA							
ZM ZW							
US 2003212138	A1	20031113	(200382)			A61K031-202	
AU 2003207535	A1	20030730	(200421)			A61K000-00	
AU 2003207535	A2	20030730	(200472)			A61K031-202	
KR 2004095207	A	20041112	(200519)			A61K031-421	
EP 1569640	A2	20050907	(200559)	EN		A61K031-425	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							

JP 2005525313 W 20050825 (200560) 109 A61K045-06

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2003059294	A2	WO 2003-US956	20030114	
US 2003212138	A1 Provisional	US 2002-348297P	20020114	<--
		US 2003-341217	20030113	
AU 2003207535	A1	AU 2003-207535	20030114	
AU 2003207535	A2	AU 2003-207535	20030114	
KR 2004095207	A	KR 2004-710888	20040713	
EP 1569640	A2	EP 2003-705746	20030114	
		WO 2003-US956	20030114	
JP 2005525313	W	JP 2003-559459	20030114	
		WO 2003-US956	20030114	

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003207535	A1 Based on	WO 2003059294
AU 2003207535	A2 Based on	WO 2003059294
EP 1569640	A2 Based on	WO 2003059294
JP 2005525313	W Based on	WO 2003059294

PRIORITY APPLN. INFO: US 2003-341217 20030113;
 US 2002-348297P
 20020114

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-202; A61K031-421; A61K031-425;
 A61K045-06

SECONDARY: A61K031-17; A61K031-19; A61K031-192; A61K031-216;
 A61K031-415; A61K031-426; A61K031-5375; A61P001-02;
 A61P001-04; A61P003-04; A61P003-06; A61P003-10;
 A61P007-02; A61P007-06; A61P009-00; A61P009-10;
 A61P011-00; A61P011-06; A61P013-12; A61P015-02;
 A61P017-00; A61P017-02; A61P017-06; A61P019-02;
 A61P021-00; A61P021-04; A61P025-04; A61P025-06;
 A61P025-28; **A61P027-02**; A61P029-00; A61P031-18;
 A61P031-22; A61P035-00; A61P037-02; A61P043-00

BASIC ABSTRACT:

WO2003059294 A UPAB: 20030906

NOVELTY - A composition comprises a peroxisome proliferator activated receptor- alpha (PPAR- alpha) agonist, a cyclooxygenase-2 (COX-2) selective inhibitor or its prodrug, and optionally a p38 **mitogen** activated protein (MAP) **kinase**, PPAR- alpha inhibitor and an excipient.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising the composition.

ACTIVITY - Analgesic; Antiinflammatory; Antipyretic; Antiarthritic; Antirheumatic; Antigout; Osteopathic; Dermatological; Immunosuppressive; Antiasthmatic; Gynecological; Antipsoriatic; Vulnerary; Gastrointestinal-Gen.; Antiulcer; Cytostatic; Anti-HIV; Respiratory-Gen.; Litholytic; Nephrotropic; Tranquilizer; Vasotropic; Antimigraine; Antithyroid; Antianemic; Antidiabetic; Neuroprotective; **Ophthalmological**; CNS-Gen.; Nootropic; Cardiovascular-Gen.; Cardiant; Antiarteriosclerotic; Thrombolytic; Cerebroprotective; Antianginal; Antibacterial; Virucide; Anorectic.

MECHANISM OF ACTION - Peroxisome proliferator activated receptor-

alpha agonist; Cyclooxygenase-2 selective inhibitor; Peroxisome proliferator activated receptor- alpha inhibitor; p38 Mitogen activated protein (MAP) kinase inhibitor.

Preferred COX-2 inhibitors have an IC50 of less than 1 (preferably less than 0.2) μ M.

USE - For treatment, prevention or inhibition of pain, inflammation, inflammation-related disorder (e.g. headache, fever, arthritis, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, asthma, bronchitis, menstrual cramps, tendinitis, bursitis, connective tissue injuries or disorders, skin related conditions, psoriasis, eczema, burns, dermatitis, gastrointestinal conditions, inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, colorectal cancer, herpes simplex infections, HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylarthritis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, **ophthalmic** diseases, pulmonary inflammation, nervous system disorders, cortical dementias, Alzheimer's disease, an **ophthalmic** disease or **ophthalmic** injury (e.g. retinitis, retinopathies, **conjunctivitis**, **uveitis**, **ocular** photophobia, acute injury to the eye tissue), arthritis (e.g. osteoarthritis, and rheumatoid arthritis)), cancer (e.g. neoplasia disorder, benign neoplasia, neoplasias in metastasis, malignant neoplasias, acral lentiginous melanoma, actinic **keratoses**, adenocarcinoma, adenoid cystic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, bartholin gland carcinoma, basal cell carcinoma, breast cancers, colon cancers, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangiocarcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epitheloid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, interepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial, metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adenocarcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma, verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor), and cardiovascular disease or disorder (e.g. coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis, venous thrombosis, angina, including unstable angina, coronary plaque inflammation, bacterial-induced inflammation, Chlamydia-induced inflammation, viral induced inflammation, inflammation associated with

surgical procedures, vascular grafting, coronary artery bypass surgery, revascularization procedures, angioplasty, stent placement, endarterectomy, and inflammation associated with other invasive procedures involving arteries, veins and capillaries), disease or disorder mediated by the activity of PPAR- α (e.g. hyperglycemia, hyperlipidemia, atherosclerosis, ischemic heart diseases, age-related disorders, dyslipidemia, insulin resistance, chronic inflammation, predisposition to atherosclerosis, tumorigenesis, hepatocarcinogenesis, atheromatous diseases, diabetes mellitus, hyperglycemia, obesity, hypertriglyceridemia, hypercholesterolemia, raising HDL levels, atherosclerosis, vascular restenosis, irritable bowel syndrome, pancreatitis, abdominal obesity, adipose cell tumors, adipose cell carcinomas, liposarcoma, disorders where insulin resistance is a component, Syndrome X, ovarian hyperandrogenism, obesity, hypoalphalipoproteinemia, type H diabetes, vascular disease, and skin wound healing) in animals (preferably humans) (all claimed).

ADVANTAGE - The composition is stable and easy to handle, and the compounds have reduced or no side effects, and are easy to prepare or administer.

Dwg. 0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B01-D02; B06-H; B07-H; B10-A08; B10-A13D; B10-B02B;
 B10-C04; B10-D03; B10-G02; B14-A02; B14-C01;
 B14-C02; B14-C03; B14-C04; B14-C09; B14-C09A;
 B14-C09B; B14-D01C; B14-D05C; B14-E08; B14-E10;
 B14-E10C; B14-E12; B14-F01; B14-F01E; B14-F02;
 B14-F02D; B14-F03; B14-F04; B14-F07; B14-H01;
 B14-J01; B14-K01; B14-K01A; B14-L01; B14-N03
 ; B14-N06B; B14-N10; B14-N11; B14-N12; B14-N13;
 B14-N17; B14-S01; B14-S04

TECH UPTX: 20030906

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The PPAR- α agonist is a medium long chain fatty acid, arylthiazolidinedione derivative, omega-3-fatty acid, unsaturated 18C fatty acid or fatty aryl, fibric acid derivative, leukotriene B₄, WY-14,643, fibric acid derivative, fibrate, clofibrate, clofibrate, fenofibrate, benzaifibrate, ciprofibrate, beclobifibrate (beclobrate), etofibrate, simfibrate, gemfibrozil, benzaifibrate (bezafibrate), (-)DRF2725, BM-17.0744, JTI-501, trichloroacetate, dichloroacetate, DHEA-S, arachidonic acid, an imidazolidinedione or thiazolidinedione derivative of formula (I), or a urea derivative of formula (II), or their salt.

Ar1 = (hetero)arylene (both optionally mono- to tetra-substituted by Ra);

Ar2 = ortho-substituted (hetero)aryl (both optionally mono- to tetra-substituted by Ra, and the ortho substituent is R);

X,Y = O, S, N-Rb, or CH₂;

Z = O or S;

n = 0 - 3;

R = 3-10C alkyl (optionally mono- to tetra-substituted by halo or 3-6C cycloalkyl), 3-10C alkenyl, or 3-8C cycloalkyl;

Ra = 1-5C alkanoyl, 1-5C alkyl, 2-15C alkenyl, 2-15C alkynyl (all optionally mono- to penta-substituted by Rc), halo, ORb, or (hetero)aryl (optionally mono- to penta-substituted by Rd);

Rb = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl (all optionally mono- to tetra-substituted by Rc), Q1, or H;

Q1 = (hetero)aryl, aryl-1-15C alkyl, heteroaryl 1-5C alkyl, 1-5C cycloalkyl, 3-8C cycloalkyl (all optionally mono- to tetra-substituted by Rd);

Rc = (hetero)aryl, or 3-8C cycloalkyl (both optionally mono- to tri-substituted by halo, or 1-6C alkyl), halo, CN, NO₂, ORf, S(O)mRf,

NRfRf, NRfCORf, NRfCO2Rf, NRfCON(Rf)2, NRfSO2Rf, CORf, CO2Rf, CON(Rf)2, SO2N(Rf)2, or OCON(Rf)2;
 m = 0 - 20;
 Rd = Rc, 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, (hetero)aryl-1-10C alkyl (all optionally substituted by Re);
 Re = halo, amino, carboxyl, 1-4C alkyl, 1-4C alkoxy, OH, aryl, aryl-1-4C alkyl, or aryloxy;
 Rf = 1-10C alkyl, 2-10C alkenyl, 2-10C alkynyl, (hetero)aryl, (hetero)aryl-1-15C alkyl, 1-15C alkanoyl, or 3-8C cycloalkyl (all optionally mono- to tetra-substituted by Re) or H;
 m = 0 - 20;
 R6 = a group of formula (i) - (iv);
 R8 = a group of formula (v) or (vi);
 y = 0 - 2;
 alk = H, or 1-6C alkyl;
 R = H, halo, cyano, -NO2, phenyl, 1-6C (fluoro)alkyl (where the alkyl group may contain heteroatoms such as N, O or S, or functional groups such as ketone or ester), or 3-7C cycloalkyl; or
 CRCR = aliphatic or aromatic ring or multi ring system (having no more than 3 alk groups);
 provided that when m is 1 or 2, then Rf is not H; and when Rc is NRfSO2Rf, then Rf is not H.
 Preferred Composition: The PPAR-alpha agonist and COX-2 selective inhibitor or its prodrug are in a wt. ratio of 0.02:1 - 200:1 (preferably 0.05:1 - 10:1).

ABEX

UPTX: 20030906

SPECIFIC COMPOUNDS - The use of 5 compounds (II) is specifically claimed, e.g. 2-(4-(2-(1-(4-biphenylethyl)-3-cyclohexylureido)ethyl)phenylthio)-2-methylpropionic acid (IIa). The COX-2 inhibitor is celecoxib, valdecoxib, deracoxib, rofecoxib, etoricoxib, parecoxib, lumiracoxib, SD-8381, ABT-963, BMS-347070, or NS-398.

ADMINISTRATION - Dosage of the PPAR-alpha agonists is 0.1 - 50 mg/kg. Dosage of the COX-2 inhibitors is 0.01 - 100 (preferably 1 - 20) mg/kg. The compounds are administered simultaneously or sequentially by enteral or parenteral routes in at least one dose per day (all claimed). Parenteral administration includes subcutaneous, intravenous, intramuscular, intrasternal, or by infusion.

EXAMPLE - A composition containing celecoxib and fenofibrate was prepared. A single dose unit of the composition contained (in mg): fenofibrate (160) and celecoxib (200).

L638 ANSWER 68 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-393329 [37] WPIX
 DOC. NO. CPI: C2003-104439
 TITLE: New aza-oxindole derivatives useful for the treatment of e.g. cancer, pain, abnormal angiogenesis including arthritis, diabetic retinopathy, macular degeneration and psoriasis.
 DERWENT CLASS: B02
 INVENTOR(S): LACKEY, K E; WOOD, E R
 PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP; (LACK-I) LACKEY K E; (WOOD-I) WOOD E R
 COUNTRY COUNT: 102
 PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG MAIN IPC
WO 2003027111	A1 20030403	(200337)* EN	22	C07D471-04

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU
 MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA
 ZM ZW

EP 1430053 A1 20040623 (200441) EN C07D471-04
 R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC
 MK NL PT RO SE SI SK TR

AU 2002334643 A1 20030407 (200461) C07D471-04
 US 2004198766 A1 20041007 (200466) C07D471-02
 JP 2005508337 W 20050331 (200523) 73 C07D471-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003027111	A1	WO 2002-US30150	20020924 <--
EP 1430053	A1	EP 2002-799606	20020924 <--
		WO 2002-US30150	20020924 <--
AU 2002334643	A1	AU 2002-334643	20020924 <--
US 2004198766	A1	WO 2002-US30150	20020924 <--
		US 2004-490831	20040325
JP 2005508337	W	WO 2002-US30150	20020924 <--
		JP 2003-530699	20020924 <--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1430053	A1 Based on	WO 2003027111
AU 2002334643	A1 Based on	WO 2003027111
JP 2005508337	W Based on	WO 2003027111

PRIORITY APPLN. INFO: **US 2001-326012P**
20010927

INT. PATENT CLASSIF.:

MAIN: C07D471-02; C07D471-04
 SECONDARY: A61K031-437; A61K031-4745; A61P001-16; A61P003-10;
 A61P007-00; A61P009-00; A61P009-10; A61P013-12;
 A61P017-06; A61P017-14; A61P019-02; A61P025-04;
 A61P025-28; A61P029-00; A61P035-00; A61P037-06;
 C07D471-12

BASIC ABSTRACT:

WO2003027111 A UPAB: 20030612

NOVELTY - Aza-oxindole derivatives (I), their salts, solvates or functional derivatives are new.

DETAILED DESCRIPTION - Aza-oxindole derivatives of formula (I), their salts, solvates or functional derivatives are new.

X, Z = N or CH;

R = H or halo (preferably H, bromo or chloro);

A = a group of formula (a) or (b);

R1 = halo;

R2 = H, 1-6C alkyl, 1-6C alkoxy or 1-6C alkylsulfanyl;

R3 = H or 1-6C alkyl.

Provided that when X is N, then Z is CH and when X is CH, then Z is N.

An INDEPENDENT CLAIM is also included for the use of (I) in the manufacture of a medicament for the treatment of a disorder mediated by

inappropriate TrkA activity.

ACTIVITY - Cytostatic; Analgesic; Antiarthritic; Antidiabetic; Ophthalmological; Antipsoriatic; Immunosuppressive; Thrombolytic; Anticoagulant; Endocrine-Gen.; Depilatory; Vasotropic; Antiarteriosclerotic; Antirheumatic; Hepatotropic; Nephrotropic; Respiratory-Gen.; Antiinflammatory; Neuroprotective; Keratolytic

MECHANISM OF ACTION - TrkA Tyrosine kinase inhibitor.

The tyrosine kinase activity of (3Z)-3-((1-methyl-1H-indole-3-yl)-methylene)-1,3-dihydro-2H-pyrrolo(3,2-b)pyridin-2-one (B) (0.0001 - 1 micro M) was measured using a synthetic peptide substrate (Sre peptide, NH₂-RRRAAAEEIYGEI-NH₂) (60 micro M). The enzyme was a GST-fusion of the intracellular domain expressed in SF9 cells. The enzyme was expressed and purified by Regeneron. The enzyme was preincubated at room temperature with cold ATP (30 micro M) and Mg to allow autophosphorylation prior to running the screen. This increased the initial rate of catalysis about 3 fold. The assay was performed in 96 well microtitre plates, using TrKA (20 - 40 nM), ATP (30 micro M), Sre peptide (50 micro M), MOPS (3-N-morpholino propane sulfonic acid) (50 mM), pH 7.5, MgCl₂ (10 mM), ³³P ATP (0.6 micro Ci) and reaction products were detected following filtration through Millipore p81 phosphocellulose plates. The assay was terminated by adding 50% phosphoric acid (100 micro l). The IC₅₀ value of (B) was found to be less than 0.010 micro M.

USE - In the manufacture of a medicament for the treatment of a disorder mediated by inappropriate TrkA activity or inappropriate mitogen activated kinase activity e.g. pain, cancer (claimed), abnormal angiogenesis (such as arthritis, diabetic retinopathy, macular degeneration and psoriasis), organ transplant rejection, tumor growth, thrombosis, chemotherapy-induced mucositis, radiation-induced mucositis, plantar-palmar syndrome, chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia and hirsutism, mucocitis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic cirrhosis, glomerulonephritis, diabetic neuropathy, malignant nephrosclerosis, chronic obstructive pulmonary disease, thrombotic microangiopathy, agglomerulopathy, diabetes mellitus, inflammation, neurodegenerative disease, actinic keratosis and hyperproliferative disorders.

ADVANTAGE - (I) selectively inhibit the catalytic activity of TrkA and other Trk family kinases thus providing new treatment strategies for those affected with cancer and chronic pain. (I) also enhance normal physiological function.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D05; B14-C01; B14-C09B; B14-D06; B14-F02; B14-F04; B14-F07; B14-G02C; B14-H01; B14-J01; B14-K01; B14-N03; B14-N10; B14-N12; B14-N17; B14-N17C; B14-R02; B14-S04

TECH UPTX: 20030612

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Three methods for the preparation of (I) are given e.g.

(1) treating 7-azaindole with brominating agent such as Br₂ under basic aqueous conditions in a suitable solvent to obtain an intermediate compound 3,3,5-tribromo-1,3-dihydro-pyrrolo(2,3-b)pyridin-2-one (II); (2) selectively reducing (II) with activated zinc in the presence of saturated ammonium chloride in a suitable solvent to obtain 5-bromo-1,3-dihydro-pyrrolo(2,3-b)pyridin-2-one (III); and (3) mixed aldol condensation reaction with HCl in a suitable solvent such as acetic acid at elevated temperature of 50 - 100degreesC of (III) and substituted biphenyl-3-carbaldehyde derivative (IV) to give (I) where A is

group (a), R1 is Br, R2 is Z1, R is Br, Z is CH, and X is N.

ABEX UPTX: 20030612

SPECIFIC COMPOUNDS - 5 Compounds (I) are specifically claimed, e.g. 3-((1-methyl-1H-indole-3-yl)-methylene)-1,3-dihydro-2H-pyrrolo(3,2-b)pyridin-2-one (Ia).

ADMINISTRATION - (I) is administered orally (including buccally or sublingually), nasally, **ophthalmically**, otically, rectally, topically, intravenously (including both bolus and infusion), intraperitoneally, intraarticularly, subcutaneously, intramuscularly by inhalation or insufflation. The oral dosage is 0.1 - 100 mg/kg or 1 - 250 mg (preferably 1 - 10 mg/kg or 25 - 250 mg). A daily dosage for 70kg mammal is 70 mg - 7 g.

EXAMPLE - Sodium hydride (5.57 g) was washed with hexanes under nitrogen before the addition of dimethylsulfoxide (DMSO) (115 ml). Diethyl malonate (22.3 g) was added dropwise over 20 minutes and the mixture was stirred for an additional 30 minutes at room temperature. 2-Chloro-3-nitropyridine (10 g) was added to the reaction mixture at 100degreesC for 15 minutes. After work up, diethyl(3-nitropyridin-2-yl)-malonate (A) was obtained. (A) (12.5 g) was dissolved in DMSO (150 ml) and water (0.79 ml) and lithium chloride (4.65 g) were added at room temperature under nitrogen. The reaction was warmed to 100degreesC for 2 hours and more lithium chloride (1 g) was added to the reaction mixture. After work up, ethyl 2-(3-nitro-pyridin-2-yl)-acetate (A1) was obtained. (A1) (8.6 g) was dissolved in ethanol (200 ml) and added to Pd/C (1.36 g) under argon. The reaction was placed under an atmosphere of hydrogen and stirred at room temperature for 30 minutes. After work up, ethyl 2-(3-amino-pyridin-2-yl)-acetate (A2) was obtained. (A2) (6.94 g) was dissolved in diethyl ether (100 ml) at room temperature. Hydrochloric acid (35 ml) was added and the reaction was stirred for 30 minutes. After work up, 4-azaoxindole (A3) was obtained. 1-Methylindole carboxaldehyde (0.020 g), (A3) (0.024 g), acetic acid (1.5 ml) and concentrated HCl (0.4 ml) were combined at room temperature and then warmed to 40degreesC for 16 hours. After work up, (3Z)-3-((1-methyl-1H-indole-3-yl)-methylene)-1,3-dihydro-2H-pyrrolo(3,2-b)pyridin-2-one (70%) was obtained.

L638 ANSWER 69 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-103217 [09] WPIX
 DOC. NO. CPI: C2003-025945
 TITLE: New kinase inhibitor useful e.g. for treating rheumatoid arthritis, psoriasis.
 DERWENT CLASS: B02
 INVENTOR(S): BONDINELL, W E; HOLT, D A; LAGO, M A; NEEB, M J; SEMONES, M A
 PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM CORP
 COUNTRY COUNT: 100
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002076985	A1	20021003	(200309)*	EN	32	C07D487-04	--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM							
ZW							
AU 2002248689	A1	20021008	(200432)			C07D487-04	--

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2002076985	A1	WO 2002-US8915	20020322	<--
AU 2002248689	A1	AU 2002-248689	20020322	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002248689	A1 Based on	WO 2002076985

PRIORITY APPLN. INFO: **US 2001-278091P**
20010323

INT. PATENT CLASSIF.:

MAIN: C07D487-04
 SECONDARY: A61K031-4375; A61K031-4985

BASIC ABSTRACT:

WO 200276985 A UPAB: 20030206
 NOVELTY - Kinase inhibitors are new.
 DETAILED DESCRIPTION - Kinase inhibitors of formula (I) are new.
 R1' = NRR1, OR, SR, SOR, SO2R or halo;
 R+R14 = G1;
 G1 = H or V1 (optionally substituted by at least one group A);
 V1 = 1-8C alkyl, 1-8C alkanoyl, 2-8C alkenyl, 2-8C alkynyl, 3-10C cycloalkyl, 0-3C alkylaryl, 0-3C alkylheterocyclyl or 0-3C alkylheteroaryl;
 R1+R15 = G1 or G2;
 G2 = C(=NH)R2, C(=NH)NR2R3, COR2, C(S)R2, CONR2R3, CO2R2, C(S)NR2R3, SO2R2, SO2NR2R3 or -(C=N(CH2)2-4(O)0-1-);
 A = V1, (hetero)aryloxy (all optionally substituted by at least one group D at any position) or V2;
 Y = inorganic or organic anion;
 D = V1, aryloxy, heteroaryloxy (all optionally substituted by at least one group E at any position) or V2;
 V2 = C(=NH)R2, COR2, CONR2R3, CON(O)R2R3, CONR2R3R4Y, CO2R2, C(O)SR2, C(S)R2, cyano, trifluoromethyl, NR2R3, N(O)R2R3, NR2R3R4Y, NR2COR2, NR2CONR2R3, NR2CON(O)R2R3, NR2CONR2R3R4Y, NR2CO2R2, NR2C(O)SR2, NR2SO2R2, NR2SO2NR2R3, nitro, OR2, OCF3, SR2, S(O)R2, S(O)2R2, SCF3, S(O)CF3, S(O)2CF3 or halo;
 NR+R1 and NR14+R15 = N=CR2R3, N=CR2NR2R3 or G3;
 G3 = ring having 3-7C atom (optionally containing 1 - 3 heteroatoms of N, O or S and substituted by H, 1-8C alkyl or (CH2)0 - 3 aryl);
 R2, R3, R4 = H or V1 (optionally substituted by E);
 NR2+R3, NR8+R9 and NR5+R6 = G3;
 E = V1 (optionally substituted by at least one of C(=NH)R5, COR5, CONR5R6, CON(O)R5R6, CONR5R6R7Y, CO2R5, C(O)SR5, C(S)R5, cyano, trifluoromethyl, NR5R6, N(O)R5R6, NR5R6R7Y, NR5COR5, NR5CONR5R6, NR5CON(O)R5R6, NR5CONR5R6R7Y, NR5CO2R5, NR5C(O)SR5, NR5SO2R5, NR5SO2NR5R6, nitro, OR5, OCF3, (hetero)aryloxy, SR5, S(O)R5, SO2R5, SCF3, S(O)CF3, S(O)2CF3, SO2NR5R6, SO3R5, PO3R5R6 or halo), C(=NH)R5, COR5, CONR5R6, CON(O)R5R6, CONR5R6RY, CO2R5, C(O)SR5, C(S)R5, cyano, trifluoromethyl, NR5R6, N(O)R5R6, NR5R6RY, NR5COR5, NR5CONR5R6, NR5CON(O)R5R6, NR5CONR5R6R7Y, NR5CO2R5, NR5C(O)SR5, NR5SO2R5, NR5SO2NR5R6, nitro, OR5, OCF3, aryloxy, heteroaryloxy, SR5, S(O)R5, SO2R5, SCF3, S(O)CF3, S(O)2CF3, SO2NR5R6, SO3R5, PO3R5R6 or halo;
 R5, R6, R7 = H or V1;
 R2' = H, 1-8C alkyl, COR8, CONR8R9, CO2R8, cyano, trifluoromethyl, NR8R9, N(O)R8R9, NR8R9R10Y, nitro, OR8, OCF3, SR8, S(O)R8, S(O)2R8, SCF3,

S(O)CF₃, S(O)2CF₃, SO₂NR₈R₉, SO₃R₈, PO₃R₈R₉ or halo;

R₈, R₉, and R₁₀ = H or V₁;

R₃ = 1-8C alkyl, 3-8C cycloalkyl, or (heteroaryl) (all optionally substituted by E), cyano, CONHR₁₁, CONR₈₉, CO₂R₈, NR₈₉, nitro, OR₈, H or halo;

R₁₁ = 2-hydroxyethyl, 2-(1-8C alkoxy)ethyl or 2-(R₁₂R₁₃N)ethyl;

R₁₂, R₁₃ = H or 1-8C alkyl;

Y' = N or CR₂';

Z' = NR₁₄, OH, OR₁₆, SH, SR₁₆, S(O)R₁₆, SO₂R₁₆ or halo; and

R₁₆ = V₁ optionally substituted by E.

ACTIVITY - Cytostatic; Antitumor; Antipsoriatic; Antirheumatic; Antiarthritic; Antidiabetic; **Ophthalmological**; Immunosuppressive; Dermatological; Hemostatic; Vasotropic; Antiarteriosclerotic; Hepatotropic; Nephrotropic; Antiinflammatory; Neuroprotective.

MECHANISM OF ACTION - Myt 1 kinase antagonist; Tie 2 kinase antagonist; CSBP/p38 kinase antagonist; Kinase inhibitor. Test details are given, but no specific results are given.

USE - In the treatment of a disease or disorder e.g. leukemias, cancer (e.g. solid tumor cancers and metastases, soft tissue cancers, brain cancer, esophageal cancer, stomach cancer, pancreatic cancer, liver cancer, lung cancer, bladder cancer, bone cancer, prostate cancer, ovarian cancer, cervical cancer, uterine cancer, testicular cancer, kidney cancer, head cancer or neck cancer), chronic inflammatory proliferative diseases, proliferative cardiovascular diseases, proliferative **ocular** disorders, benign hyperproliferative diseases, psoriasis, rheumatoid arthritis, diabetic retinopathy, hemangiomas or excessive or inappropriate angiogenesis and for treating a disease which is characterized by excessive or inappropriate angiogenesis in a mammal (claimed). In the manufacture of a medicament for the treatment of a disease mediated by a kinase (e.g. abl, ARaf, ATK, ATM, bcr-abl, Blk, BRaf, Brk, Btk, CDK1, CDK2, CDK3, CDK4, CDKS, CDK6, CDK7, CDK8, CDK9, cfms, c-fms, CHK1, c-kit, c-met, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, ERK, ERK1, ERK2, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, FLK-4, Fps, Frk, Fyn, GSK, gsk3a, gsk3b, Hck, IGF-IR, IKK, IKK1, LKK2, IKK3, INS-R, Integrin-linked kinase, Jak, JAK1, JAK2, JAK3, **JNK, JNK**, Lck, Lyn, MEK, MEK1, MEK2, Myt1, p38, PDGFR, PIK, PKB1, PKB2, PKB3, PKC, PKC alpha, PKC beta, PKC delta, PKC epsilon, PKC gamma, PKC lambda, PKC mu, PK psi, PLK1, Polo-like kinase, PYK2, src, tiel, tie2, TrkA, TrkB, TrkC, UL13, UL97, VEGF-R1, VEGF-R2, wee-1, Yes and Zap70. and for treating a disease organ transplant rejection, tumor growth, chemotherapy induced mucositis, radiation-induced mucositis, plantar-palmar syndrome, chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia and hirsutism, mucocitis, restenosis, atherosclerosis, rheumatoid arthritis, angiogenesis, hepatic irrrosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, chronic obstructive pulmonary disease, thrombotic microangiopathy, aglomerulopathy, psoriasis, diabetes mellitus, inflammation, a neurodegenerative disease, macular degeneration, actinic **keratosis** and hyperproliferative disorders.

ADVANTAGE - The compound antagonizes a Myt1 kinase, Tie 2 kinase or CSBP/p38 kinase receptor.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B14-C06; B14-C09B; B14-D06; B14-F01; B14-H01; B14-N03; B14-N17C

TECH UPTX: 20030206

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) (in which Z' is OR₁₆) involves:

(1) Reacting appropriately substituted 2-chloro-4,5-diaminopyrimidine of formula (Ia) with ethyl alpha-oxo carboxylic acid ester in a solvent at a temperature to obtain the substituted pteridin-7-ol of formula (Ib);
(2) Treating (Ib) with an amine at a temperature for a time to give a compound of formula (Ic);
(3) Treating (Ic) with an activating agent to give a chloro pteridine compound of formula (Id); and
(4) Treating (Id) with alcohol and a base at room temperature to obtain (I).

ABEX

UPTX: 20030206

SPECIFIC COMPOUNDS - 1 Compound is specifically claimed e.g.
6-(2,6-Dichlorophenyl)-2-((4-(2-(diethylamino)ethoxy)phenyl)amino)-7-methoxy-pteridine (IA).

ADMINISTRATION - (I) can be administered intravenously, intraperitoneally, subcutaneously, intramuscularly, orally (in a dosage of 0.01 - 500 (preferably 0.1 - 50) mg/kg), topically (in a dosage of 0.01 - 5.0%) or transdermally, parenterally, nasally or transmucosally (in a dosage of 0.01 - 100 mg/kg).

EXAMPLE - A mixture of 4,5-diamino-2-chloropyrimidine (0.14 g) and ethyl benzylformate (0.18 g) in ethanol (2 ml) was refluxed overnight, cooled, filtered and the filtrate was washed and dried to form 2-chloro-6-phenyl-pteridin-7-ol (a). (a) (10 mg) and 4-(diethylamino)butylamine (143 mg) were heated to 150degreesC for 1.5 hour, cooled and worked up to obtain 2-((4-(diethylamino)butyl)amino)-6-phenyl-pteridin-7-ol (b). (b) was treated with thionyl chloride and a trace of dimethylformamide in chloroform in chloroform to give 7-chloro-2-((4-(diethylamino)butyl)amino)-6-phenyl-pteridine (c). (c) was treated with sodium methoxide in methanol and warmed to give 2-((4-(diethylamino)butyl)amino)-7-methoxy-6-phenyl-pteridine.

DEFINITIONS - Preferred Definitions:

R'1 = NRR1;
R,R'2 = H;
R1 = phenyl;
A = OR2;
R2 = ethyl substituted on 2 position by E;
E = NR5R6;
R5,R6 = ethyl;
R'3 = phenyl optionally substituted by 2,6-dichloro;
Z' = OR16;
R16 = methyl; and
Y' = N.

L638 ANSWER 70 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-018862 [01] WPIX
DOC. NO. CPI: C2003-004632
TITLE: Use of **mitogen** activated protein kinase inhibitor or an enzyme that is a member of **mitogen** activated protein kinase family for inhibiting angiogenesis e.g. myocardial angiogenesis.
DERWENT CLASS: B04
INVENTOR(S): DUESBERY, N S; VANDE WOUDE, G F; WEBB, C P
PATENT ASSIGNEE(S): (VAND-N) VAN ANDEL INST; (DUES-I) DUESBERY N S; (WOUD-I) VANDE WOUDE G F; (WEBB-I) WEBB C P
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG MAIN IPC

WO 2002076496 A1 20021003 (200301)* EN 61 A61K038-48<--
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TR TZ UG ZM ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
 ZW
 EP 1377312 A1 20040107 (200404) EN A61K038-48
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 AU 2002255852 A1 20021008 (200432) A61K038-48<--
 US 2004136975 A1 20040715 (200447) A61K038-48

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002076496	A1	WO 2002-US8656	20020322 <--
EP 1377312	A1	EP 2002-725277	20020322 <--
		WO 2002-US8656	20020322 <--
AU 2002255852	A1	AU 2002-255852	20020322 <--
US 2004136975	A1	WO 2002-US8656	20020322 <--
		US 2004-472396	20040308

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1377312	A1 Based on	WO 2002076496
AU 2002255852	A1 Based on	WO 2002076496

PRIORITY APPLN. INFO: **US 2001-277625P**
20010322; US 2004-472396
 20040308

INT. PATENT CLASSIF.:

MAIN: A61K038-48

SECONDARY: A01N031-08; A01N037-18; A01N043-32; A01N043-50

BASIC ABSTRACT:

WO 200276496 A UPAB: 20030101

NOVELTY - Inhibiting cell migration, cell invasion, cell proliferation, angiogenesis or inducing apoptosis by contacting the cells with an inhibitor of MEK or an enzyme which is a member of **mitogen** activated protein **kinase** (MAPK) family, is new.

ACTIVITY - Antitumor; Antiarteriosclerotic; Vasotropic; Tranquilizer; Vulnerary; Thrombolytic; Cytostatic; Gynecological; Antiarthritic; Antipsoriatic; Dermatological; Antiinflammatory; Antiulcer; Antidiabetic; **Ophthalmological**; Antisickling.

MECHANISM OF ACTION - Inhibitor of cell migration; angiogenesis; cell invasion; cell proliferation.

Mice having tumor diameter of 5 - 7 mm were divided in 2 groups.

Group (A) was injected with anthrax lethal toxin (LeTx) (10 micro g protective antigen (PA) and 2 micro g anthrax lethal factor (LF)) on left side and on right side with buffered saline. Group (B) was sham-injected on the left side and on the right side with buffered saline. The treatment was continued for 5 days. The results showed that average mass of group (A)/(B) tumor was 1.35 plus or minus 0.77/3.67 plus or minus 1.25.

USE - For inhibiting angiogenesis, neovascularization, tumor (e.g. solid tumor or brain tumor); for treating atherosclerosis, myocardial angiogenesis, angiofibroma, arteriovenous malformation, post-balloon

angioplasty vascular restenosis, vascular adhesion, neointima formation following vascular trauma, vascular graft restenosis, coronary collateral formation, deep venous thrombosis, lung fibrosis, chemotherapy-induced fibrosis, wound healing with scarring, fibrosis, hypertrophic scar, endometriosis, uterine adenomyosis, hemangioma, arthritis, psoriasis, pyogenic granuloma, delayed wound healing, nonunion fracture, Osler-Weber syndrome, scleroderma, trachoma, fibrosis associated with chronic inflammatory condition, telangiectasia, Von-Hippel-Landau syndrome, peptic ulcer or keloids; for treating disease e.g. proliferative diabetic retinopathy, neovascular age-related macular degeneration, retinopathy of prematurity, sickle cell retinopathy, retinal vein occlusion, neovascular glaucoma, retrolental fibroplasia, uveitis, choroidal neovascularization, iris neovascularization or **corneal** graft neovascularization (all claimed).

ADVANTAGE - MEK inhibitor or the enzyme which is a member of MAPK family stops growth by reducing the size or growth rate of tumor or destruction of tumor, or by a measurable regression of a primary or metastatic tumor.

Dwg.0/4

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; DCN
MANUAL CODES: CPI: B04-L01; B14-C03; B14-C09; B14-E08; B14-F01;
B14-F02; B14-H01; B14-N01; **B14-N03**;
B14-N17B; B14-N17C

TECH UPTX: 20030101

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The inhibitor of MEK is an MEK-directed protease (preferably Bacillus anthracis lethal factor or its functional derivative). The inhibitor of MAPK family member is extracellular signal regulated kinase (ERK)1, ERK2, p38 kinase or **JNK** (preferably p38 kinase). Preferred Method: The contacting is carried out in vivo.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The inhibitor is an organic small molecule (preferably PD98059, U0126, SB203580 or PD184352).

ABEX UPTX: 20030101

ADMINISTRATION - Dosage comprises 1 ng - 100 mg/kg body weight of MER inhibitor and administered orally, parenterally, topically, transdermally, intravaginally, intrapenile, intranasally, intrabronchially, intracranially, intraocularly, intraaurally or rectally.

EXAMPLE - No relevant example given.

L638 ANSWER 71 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-723166 [78] WPIX
DOC. NO. CPI: C2002-204660
TITLE: New 6-substituted pyrido pyrimidine derivatives as e.g. **mitogen-activated protein (MAP) kinase** inhibitors useful in treating e.g. arthritis, Alzheimer's disease and irritable bowel syndrome.
DERWENT CLASS: B02
INVENTOR(S): CHEN, J J; DUNN, J P; GOLDSTEIN, D M; STAHL, C M;
COLDSTEIN, D M
PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (CHEN-I) CHEN J J;
(DUNN-I) DUNN J P; (GOLD-I) GOLDSTEIN D M; (STAHL-I) STAHL C M; (SYNT) SYNTEX USA LLC
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND DATE	WEEK	LA	PG MAIN IPC
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WO 2002064594  A2 20020822 (200278)* EN 207 C07D487-04<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
    NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W:  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
    DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
    KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
    RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
US 2003171584  A1 20030911 (200367)          C07D475-02
NO 2003003540  A 20030811 (200373)          C07D471-04
EP 1361880     A2 20031119 (200377)  EN      A61K031-519
R:  AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
    RO SE SI TR
HU 2003003458  A2 20040128 (200415)          A61K031-519
US 6696566     B2 20040224 (200415)          C07D475-00
BR 2002007172  A 20040330 (200424)          C07D487-04
AU 2002256615  A1 20020828 (200427)          C07D487-04<--
US 2004116698  A1 20040617 (200440)#          C07D471-02
KR 2004018254  A 20040302 (200443)          C07D471-04
CZ 2003002416  A3 20040714 (200448)          C07D471-04
JP 2004525896  W 20040826 (200456)          369 C07D471-04
CN 1503672     A 20040609 (200460)          A61K031-519
SK 2003001132  A3 20041005 (200467)          C07D487-04
MX 2003007166  A1 20031201 (200470)          C07D471-04
ZA 2003005938  A 20050126 (200513)          220 A61K000-00
NZ 526961      A 20050324 (200523)          C07D487-04

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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002064594	A2	WO 2002-EP1106	20020204 <--
US 2003171584	A1 Provisional	US 2001-268375P	20010212 <--
	Provisional	US 2001-334654P	20011130 <--
		US 2002-73845	20020211 <--
NO 2003003540	A	WO 2002-EP1106	20020204 <--
		NO 2003-3540	20030811
EP 1361880	A2	EP 2002-726103	20020204 <--
		WO 2002-EP1106	20020204 <--
HU 2003003458	A2	WO 2002-EP1106	20020204 <--
		HU 2003-3458	20020204 <--
US 6696566	B2 Provisional	US 2001-268375P	20010212 <--
	Provisional	US 2001-334654P	20011130 <--
		US 2002-73845	20020211 <--
BR 2002007172	A	BR 2002-7172	20020204 <--
		WO 2002-EP1106	20020204 <--
AU 2002256615	A1	AU 2002-256615	20020204 <--
US 2004116698	A1 Cont of	US 2002-73845	20020211 <--
		US 2003-722703	20031125
KR 2004018254	A	KR 2003-710562	20030811
CZ 2003002416	A3	WO 2002-EP1106	20020204 <--
		CZ 2003-2416	20020204 <--
JP 2004525896	W	JP 2002-564525	20020204 <--
		WO 2002-EP1106	20020204 <--
CN 1503672	A	CN 2002-804834	20020204 <--
SK 2003001132	A3	WO 2002-EP1106	20020204 <--
		SK 2003-1132	20020204 <--
MX 2003007166	A1	WO 2002-EP1106	20020204 <--
		MX 2003-7166	20030811
ZA 2003005938	A	ZA 2003-5938	20030731

NZ 526961	A	NZ 2002-526961	20020204	<--
		WO 2002-EP1106	20020204	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1361880	A2 Based on	WO 2002064594
HU 2003003458	A2 Based on	WO 2002064594
BR 2002007172	A Based on	WO 2002064594
AU 2002256615	A1 Based on	WO 2002064594
US 2004116698	A1 Cont of	US 6696566
CZ 2003002416	A3 Based on	WO 2002064594
JP 2004525896	W Based on	WO 2002064594
SK 2003001132	A3 Based on	WO 2002064594
MX 2003007166	A1 Based on	WO 2002064594
NZ 526961	A Based on	WO 2002064594

PRIORITY APPLN. INFO: **US 2001-334654P**
20011130; US
2001-268375P 20010212;
US 2002-73845
20020211; US 2003-722703
20031125

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-519; C07D471-02; C07D471-04;
C07D475-00; C07D475-02; C07D487-04

SECONDARY: A61K031-4375; A61K031-4745; A61K031-535; A61K031-5377;
A61P001-04; A61P009-00; A61P011-00; A61P017-00;
A61P017-06; A61P019-02; A61P025-00; A61P025-28;
A61P029-00; A61P037-00; C07D487-02; C07D519-00

INDEX: C07D221:00; C07D239:00; C07D471-04; C07D221:00,
C07D239:00, C07D471-04

BASIC ABSTRACT:

WO 200264594 A UPAB: 20021204

NOVELTY - 6-Substituted pyrido pyrimidine derivatives are new.

DETAILED DESCRIPTION - 6-Substituted pyrido pyrimidine derivatives of formula (I), (II), or their salts are new;

Z' = N or CH;

W = NR2 or O;

X1 = O, NR4, S, CR5R6 or C(O);

R4 - R7, R32, R34 and R35 = H or alkyl;

X2 = O or NR7;

Ar1 = (hetero)aryl;

R2 = H, alkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, heteroalkylcarbonyl, heteroalkyloxycarbonyl or -R21-R22;

R21 = alkylene or -C(O)-;

R22 = alkyl or alkoxy;

R1 = T, haloalkyl, heteroaryl, heteroaralkyl, heteroalkylsubstituted cycloalkyl, heterosubstituted cycloalkyl, cyanoalkyl, heterocyclyl, heterocyclylalkyl, R12-SO2-heterocycloamino, -Y1-C(O)-Y2-R11, (heterocyclyl)(cycloalkyl)alkyl or (heterocyclyl)(heteroaryl)alkyl;

T = H, (hetero)alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl;

R12 = haloalkyl, (hetero)aryl or (hetero)aralkyl;

Y1 and Y2 = absent or alkylene group;

R11 = R31, haloalkyl;

R31 = H, alkyl, OH, alkoxy, amino, monoalkylamino or dialkylamino;

R3 = T, haloalkyl, cyanoalkyl, alkylene-C(O)-R31, amino, monoalkylamino, dialkylamino, NR32-Y3-R33 or acyl;

Y3 = -C(O), -C(O)O-, -C(O)NR34, S(O)2 or S(O)2NR35;

R33 = H, (hetero)alkyl, cycloalkyl, cycloalkylalkyl or optionally substituted phenyl;

R8 and R9 = T, alkylsulfonyl, arylsulfonyl, -C(O)-R81;

R81 = (hetero)alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryloxy, amino, mono- or di-alkylamino, arylamino or aryl(alkyl)amino;

R8+R9 = CR82R83;

R82 and R83 = H, alkyl, cycloalkyl, cycloalkylalkyl, or optionally substituted phenyl.

INDEPENDENT CLAIMS are also included for:

(1) Preparation of (I);

(2) Preparation of a sulfide compound of formula (III) comprising contacting an aldehyde of formula (Ia) with an aryl compound of formula Ar1-X1-X3 under conditions to give (III);

(3) Intermediates of formula (IV) and (V);

(4) Use of (I) for the preparation of a medicament for treating p38 mediated disorders.

X3 = -C(O)-OR';

R' = alkyl;

W' = S, S(O), S(O)₂ or O;

R10 = alkyl, aryl, aralkyl, cycloalkyl or cycloalkylalkyl;

R10+W' = leaving group of OH.

ACTIVITY - Antiarthritic; Antiinflammatory; Nootropic; Neuroprotective; Antipyretic; Antirheumatic; Osteopathic; Antiasthmatic; Antibacterial; Immunosuppressive; Virucide; Protozoacide; Immunomodulator; Anti-HIV; Antiarteriosclerotic; Thrombolytic; Cardiant; Virucide; Cytostatic; Antidiabetic; Antipsoriatic; Dermatological; Vulnerary; Antiulcer; Ophthalmological.

MECHANISM OF ACTION - Mitogen-activated protein (MAP) kinase (preferably p38) inhibitor; Tumor necrosis factor (TNF- alpha) release inhibitor.

A solution 6-(2,4-difluorophenoxy)-8-methyl-2-(tetrahydro-2H-pyran-4-ylamino)pyrido(2,3-d)pyrimidin-7(8H)-one (A) in DMSO was added to p38 kinase diluted in kinase buffer. The samples were incubated for 10 minutes at 30 deg. C. The kinase reaction was initiated by the addition of a substrate cocktail containing myelin basic protein (MBP) and gamma-phosphate form-ATP. After incubating for additional 20 minute at 30 deg. C, the reaction was terminated by adding 0.75% phosphoric acid. The IC50 value for (A) was found to be 0.006 micro M.

USE - Useful in the treatment of arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease, Alzheimer's disease (all claimed). Also useful in treating inflammation, fever, arthritis, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, gouty arthritis, pulmonary disorders or lung inflammation, adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, chronic pulmonary inflammatory disease, viral, bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, bone resorption diseases (e.g. osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease, graft vs. host reaction, allograft rejections, cardiovascular diseases, atherosclerosis, thrombosis, congestive heart failure, cardiac reperfusion injury, renal reperfusion injury, liver disease, nephritis, myalgias, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus (SLE), skin-related conditions (e.g. psoriasis, eczema, burns, dermatitis, keloid formation, and scar tissue formation), gastrointestinal conditions (e.g. inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and

ulcerative colitis), ophthalmic diseases (e.g. retinitis, retinopathies, uveitis, ocular photophobia, and acute injury to the eye tissue), angiogenesis, neoplasia, metastasis, ophthalmological conditions (e.g. corneal graft rejection, ocular neovascularization, retinal neovascularization, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma), ulcerative diseases (e.g. gastric ulcer, pathological), non-malignant conditions (e.g. hemangiomas, infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone, diabetic nephropathy, cardiomyopathy), disorders of the female reproductive system (e.g. endometriosis); treatment of companion animals, exotic animals, farm animals (including mammals, rodents, etc.)

ADVANTAGE - The compounds are highly potent and selective against p38 kinase relative to cyclin dependent kinases and tyrosine kinases.

Dwg.0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-D06; B06-D08; B14-A01; B14-A02; B14-A03B;
 B14-C02; B14-C03; B14-C04; B14-C09; B14-D06;
 B14-E08; B14-E10; B14-E10C; B14-F01; B14-F02F2;
 B14-F04; B14-F05; B14-F07; B14-G01B; B14-G02C;
 B14-G02D; B14-H01; B14-J01A4; B14-K01; B14-L06;
 B14-N01; B14-N03; B14-N04; B14-N05;
 B14-N10; B14-N12; B14-N14; B14-N16; B14-N17;
 B14-S01; B14-S04; B14-S06

TECH UPTX: 20021204
 TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises contacting a compound of formula (Ic) with an amine of formula R1R2NH under nucleophilic displacement conditions to give (I).
 L = leaving group.

ABEX UPTX: 20021204
 SPECIFIC COMPOUNDS - 6 Compounds are specifically claimed as (I) e.g. 6-(2,4-difluorophenoxy)-8-methyl-2-(tetrahydro-2H-pyran-4-ylamino)pyrido(2,3-d)pyrimidin-7(8H)-one (A).

ADMINISTRATION - The compounds are administered in a dosage of 0.1 - 100 mg/kg/day as a single or divided dose. The compounds are administered orally, nasally, rectally or parenterally.

EXAMPLE - A mixture of 7-Chloro-3-(2,4-difluorophenoxy)-1-methyl-1H-(1,6)naphthyridin-2one (2.06 g) and 4-aminotetrahydropyran (3.4 g) was heated to 150-160degreesC for 3 days. The reaction mixture was cooled, and worked-up to give 6-(2,4-difluorophenoxy)-8-methyl-2-(tetrahydro-2H-pyran-4-ylamino)pyrido(2,3-d)pyrimidin-7(8H)-one (A; 1.3g).

DEFINITIONS - Preferred Definitions:

R2 = acyl or acetyl;
 Z = N;
 W = NH;
 X1 = O;
 R1 = heterocyclyl, heteroalkyl, hydroxyalkyl;
 Ar1 = 2,4-difluorophenyl;
 R3 = methyl, propyl or cyclopropyl;
 R8 = H;
 R9 = alkyl, alkylsulfonyl or -C(O)-R81;
 R81 = alkyl, alkoxy, aryloxy, amino, monoalkylamino or dialkylamino.

L638 ANSWER 72 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-383042 [41] WPIX
 DOC. NO. CPI: C2002-107926
 TITLE: New oxindole derivatives are protein kinase inhibitors

used for treating e.g. tumors, pain, restenosis,
atherosclerosis and thrombosis.

DERWENT CLASS: B02

INVENTOR(S): HARRIS, P A; HUNTER, R N; KUYPER, L F; LACKEY, K E;
MCNUTT, R W; PEEL, M R; WOOD, E R

PATENT ASSIGNEE(S): (GLAX) GLAXO GROUP LTD; (HARR-I) HARRIS P A; (KUY-P-I)
KUYPER L F; (LACK-I) LACKEY K E; (MCNU-I) MCNUTT R W;
(PEEL-I) PEEL M R; (WOOD-I) WOOD E R

COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002020513	A1	20020314	(200241)*	EN	72	C07D403-12	--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW							
AU 2001086647	A	20020322	(200251)			C07D403-12	--
EP 1317446	A1	20030611	(200339)	EN		C07D403-12	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR							
US 2003225090	A1	20031204	(200380)			A61K031-53	
JP 2004508366	W	20040318	(200420)		117	C07D209-34	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002020513	A1	WO 2001-US26286	20010823 <--
AU 2001086647	A	AU 2001-86647	20010822 <--
EP 1317446	A1	EP 2001-966107	20010823 <--
		WO 2001-US26286	20010823 <--
US 2003225090	A1	WO 2001-US26286	20010823 <--
		US 2003-362739	20030227
JP 2004508366	W	WO 2001-US26286	20010823 <--
		JP 2002-525134	20010823 <--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001086647	A Based on	WO 2002020513
EP 1317446	A1 Based on	WO 2002020513
JP 2004508366	W Based on	WO 2002020513

PRIORITY APPLN. INFO: **US 2000-229966P**
20000901; US 2003-362739
 20030227

INT. PATENT CLASSIF.:

MAIN: A61K031-53; C07D209-34; C07D403-12

SECONDARY: A61K031-135; A61K031-404; A61K031-405; A61K031-4184;
 A61K031-4196; A61K031-4245; A61K031-454; A61P007-02;
 A61P009-10; A61P029-00; A61P029-02; A61P035-00;
 A61P043-00; C07D209-14; C07D401-12; C07D403-02;
 C07D487-02; C07D487-04

BASIC ABSTRACT:

WO 200220513 A UPAB: 20020701

NOVELTY - Oxindole derivatives (I) are new.

DETAILED DESCRIPTION - Oxindole derivatives of formula (I) and their salts, solvates, and physiological functional derivatives are new.

R1, R2 = H; or

R1 + R2 = a fused ring Het;

Het = triazine ring;

R3 = H;

R4 = H, CH₂-C(O)NH₂, or a group of formula (i)-(iii);

R5 = H or a group of formula (iv) or

R4 + R5 = a fused cyclic urea ring, and

R6-R8 = H.

ACTIVITY - Analgesic; Cytostatic; Antiarthritic; Antidiabetic; **Ophthalmological**; Antipsoriatic; Dermatological; Immunosuppressive; Hemostatic; Immunostimulant; Depilatory; Vasotropic; Antiarteriosclerotic; Antirheumatic; Hepatotropic; Nephrotropic; Thrombolytic; Anticoagulant; Neuroprotective; **Keratolytic**.

MECHANISM OF ACTION - Trk family protein kinase inhibitor; **Mitogen** activated kinase inhibitor.

A test for inhibition of TrkA kinase enzyme was carried out using a synthetic peptide substrate (Src peptide NH₂-RRRAAAEEIYGEI-NH₂). The enzyme was a GST-fusion of the intracellular domain expressed in SF9 cells. The enzyme was expressed and purified by Regeneron. The enzyme was preincubated with cold ATP and Mg to allow autophosphorylation prior to running the screen. This increased the initial rate of catalysis 3 fold. The assay was performed in 96 well microtiter plates, and reaction products were detected following filtration through Millipore p81 phosphocellulose plates.

Results showed that 5-(((Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl)amino)-1,3-dihydro-2H-benzimidazol-2-one (Ia) exhibited an IC₅₀ value of upto 0.01 μ M for TrkA tyrosine kinase inhibition.

USE - Used for treating pain, cancer, abnormal angiogenesis e.g. arthritis, diabetic retinopathy, macular degeneration and psoriasis, organ transplant rejection, tumor growth, chemotherapy-induced mucositis, radiation-induced mucositis, planter-palmar syndrome, chemotherapy-induced alopecia, chemotherapy-induced thrombocytopenia, chemotherapy-induced leukopenia and hirsutism, restenosis, atherosclerosis, rheumatoid arthritis, hepatic cirrhosis, glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, chronic obstructive pulmonary disease, thrombotic microangiopathy, aglomerulopathy, diabetes mellitus, inflammation, a neurodegenerative disease, macular degeneration, actinic **keratosis** and hyperproliferative disorders.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D01; B06-D17; B14-C01; B14-C03; B14-C09B; B14-D07; B14-F01G; B14-F04; B14-F07; B14-G02C; B14-H01; B14-H02; B14-J01A4; B14-J05; B14-N03; B14-N10; B14-N16; B14-N17C; B14-R02; B14-S04

TECH UPTX: 20020701

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises e.g. reacting an oxindole compound of formula (IV) with an aniline compound of formula (V).

L = NMe₂, OEt or OH.

ABEX UPTX: 20020701

WIDER DISCLOSURE - Also stated to be new are oxindole compounds of formula (I') and their salts, solvates, polymorphs, physiologically functional derivatives, including esters, amides, carbamates, solvates, hydrates, affinity reagents and prodrugs in either crystalline or amorphous form, where the esters, amides and carbamates are preferably hydrolyzable and

more preferably are biohydrolyzable.

Y, Z, A, D = C or N;

X = N, CH, CCF3 or 1-12C aliphatic group;

R1a = H, 1-12C aliphatic group, thiol, OH, OH-1-12C aliphatic group, aryl, aryl-1-12C aliphatic group, R9-aryl-1-12C aliphatic group, Cyc, Cyc-1-6C aliphatic group, Het, Het-1-12C aliphatic group, 1-12C alkoxy, aryloxy, amino, 1-12C aliphatic amino, di-1-12C aliphatic amino, di-1-12C aliphatic aminocarbonyl, di-1-12C aliphatic aminosulfonyl, 1-12C alkoxycarbonyl, Fl, B, I, CN, sulfonamide or nitro;

R2a = H, 1-12C aliphatic group, N-hydroxyimino-1-12C aliphatic group, 1-12C alkoxy, OH-1-12C aliphatic group, 1-12C alkoxycarbonyl, carboxy 1-12C aliphatic, aryl, R9-aryl-oxycarbonyl, R9-oxycarbonyl-aryl, Het, aminocarbonyl, 1-12C aliphatic-aminocarbonyl, aryl-1-12C aliphatic-aminocarbonyl, R9-aryl-1-12C aliphatic-aminocarbonyl, Het-1-12C aliphatic-aminocarbonyl, OH-1-12C aliphatic-aminocarbonyl, 1-12C alkoxy-1-12C aliphatic-aminocarbonyl, 1-12C alkoxy-1-12C aliphatic-amino, di-1-12C aliphatic amino, di-1-12C aliphatic aminocarbonyl, di-1-12C aliphatic aminosulfonyl, halo, OH, 1-12C aliphatic-sulfonyl, aminosulfonyl or 1-12C aliphatic-aminosulfonyl, or

R1a + R2a = Het optionally substituted by 1-12C aliphatic group, halo, NO2, CN, 1-12C alkoxy, amino, hydroxy, NR10R11 or oxo;

R3a = H, 1-12C aliphatic group, OH, OH 1-12C aliphatic group, di-1-12C aliphatic amino, di-1-12C aliphatic aminocarbonyl, di-1-12C aliphatic aminosulfonyl, 1-12C alkoxy, aryl, aryloxy, OH-aryl, Het, OH-Het, Het-oxy or halo, or

R2a + R3a = Het optionally substituted by 1-6C aliphatic group or 1-6C aliphatic-carbonyl;

R4a-R6a = H, 1-12C aliphatic group, thiol, 1-6C aliphatic-thio, di(trifluoromethyl)hydroxymethyl, carboxamide, mono-1-12C aliphatic aminocarbonyl, OH, OH-1-12C aliphatic, aryl, aryl-1-12C aliphatic group, R9-aryl-1-12C aliphatic group, Cyc, Cyc-1-6C aliphatic group, Het, Het-1-12C aliphatic group, 1-12C alkoxy, aryloxy, Het-oxy, amino, NR10R11-1-12C aliphatic aminocarbonyl, NR10R11-1-12C aliphatic alkoxycarbonyl, NR10R11-1-12C aliphatic aminocarbonylamino, NR10R11-1-6C aliphatic alkoxycarbonylamino, NR10R11-1-6C aliphatic sulfonyl, Het-1-6C aliphatic aminocarbonyl, Het-1-6C aliphatic aminocarbonylamino, Het-1-6C alkoxycarbonylamino, Het-1-6C aliphatic carbonyl, Het-1-6C alkoxycarbonyl, 1-6C aliphatic sulfonyl-1-6C aliphatic aminoalkyl, 1-6C aliphatic sulfonyl-1-6C aliphatic aminoalkyl-Het-, 1-6C alkoxycarbonyl, 1-6C aliphatic carbonylamino, (1-6C aliphatic carbonyl)(1-6C aliphatic)amino, NR10R11-1-6C aliphatic carbonylamino, NR10R11-1-6C aliphatic carbonyl 1-6C aliphatic amino, NR10R11-1-6C aliphatic sulfonylamino, NR10R11-1-6C aliphatic sulfonyl 1-6C aliphatic amino, halo, cyano, diethoxyphosphorylmethyl, nitro, trifluoromethyl or trifluoromethoxy;

R7a, R8a = H, halo, 1-2C alkoxy, 1-3C aliphatic group;

R7a = optionally fused to R5a to form a fused benzo ring from the R5a to the R7a positions;

R4a = optionally fused to R5a to form a fused cyclic urea ring from the R4a to the R5a positions;

R9 = 1-12C aliphatic group, OH, 1-12C alkoxy or halo;

R10, R11 = H, 1-6C aliphatic group or Het;

aryl = phenyl, naphthyl, phenanthryl or anthracenyl;

Cyc = cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl, and optionally has one or more degrees of unsaturation, and

Het = benzimidazole, dihydrothiophene, dioxin, dioxane, dioxolane, dithiane, dithiazine, dithiazole, dithiolane, furan, imidazole, isoquinoline, morpholine, oxazole, oxadiazole, oxathiazole, oxathiazolidine, oxazine, oxadiazine, piperazine, piperidine, pyran, pyrazine, pyrazole, pyridine, pyrimidine, pyrrole, pyrrolidine, quinoline, tetrahydrofuran, tetrazine, thiadiazine, thiadiazole, thiazine, thiazole,

thiomorpholine, thiophene, thiopyran, triazine, and triazole (all optionally substituted by 1-12C aliphatic group, OH, 1-12C alkoxy, NR10R11, NR10R11-1-12C aliphatic group, NR10R11-1-12C aliphatic amino, oxo or dioxo,

provided that:

(1) Z and D may be N, but otherwise no more than one of Y, Z, A and D may be N;

(2) when Y, Z, or A are N, R1a-R3a are not present;

(3) when X is N, R3a is not Cl or 3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl;

(4) when X is N, R3a is not F and R4a-R6a are not NO₂, and

(5) R4a-R8a are not simultaneously H.

Preparation: Preparation of (I') comprises reacting an oxindole compound of formula (II) with an aniline compound of formula (III) to give (I'; X = N).

L = NMe₂, OEt or OH.

SPECIFIC COMPOUNDS - 6 Compounds (I) are specifically claimed e.g:

5-((Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl)amino)-1,3-dihydro-2H-benzimidazol-2-one (Ia).

ADMINISTRATION - The dosage is 0.1-100 (preferably 1-10) mg/kg/day orally.

EXAMPLE - A solution of 161 mg of 3-(hydroxymethylene)-1,3-dihydro-2H-indol-2-one, 149 mg of 5-aminobenzimidazolone, and 5 ml of ethanol was heated at 55degreesC for 1.5 hours. The resulting solid was isolated by filtration and recrystallized from dimethylsulfoxide/methanol to give 5-((Z)-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl)amino)-1,3-dihydro-2H-benzimidazol-2-one (Ia) (150 mg; 51%).

L638: ANSWER 73 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-304240 [34] WPIX
 CROSS REFERENCE: 2002-489654 [52]
 DOC. NO. CPI: C2002-088503
 TITLE: New 7-oxo-pyridopyrimidine derivatives are p38
 mitogen activated protein kinase
 inhibitors used for treating e.g. arthritis, Alzheimer's
 disease, bacterial infections and malaria.
 DERWENT CLASS: B02
 INVENTOR(S): CHEN, J J; DUNN, J P; GOLDSTEIN, D M; LIM, J A; ARZENO, H
 B
 PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (ARZE-I) ARZENO H B;
 (CHEN-I) CHEN J J; (DUNN-I) DUNN J P; (GOLD-I) GOLDSTEIN
 D M; (LIMJ-I) LIM J A; (SYNT) SYNTEX USA LLC
 COUNTRY COUNT: 98
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002018380	A1	20020307	(200234)*	EN	135	C07D471-04<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO							
RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW							
US 2002055513	A1	20020509	(200235)			A61K031-519<--	
AU 2001093784	A	20020313	(200249)			C07D471-04<--	
US 2002137756	A1	20020926	(200265)			A61K031-519<--	
US 6506749	B2	20030114	(200313)			C07D471-04	
US 6518276	B2	20030211	(200314)			A61K031-519	

EP 1315726 A1 20030604 (200337) EN C07D471-04
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 KR 2003022422 A 20030315 (200350) C07D471-04
 US 2003144307 A1 20030731 (200354) # A61K031-519
 US 2003153586 A1 20030814 (200355) # A61K031-519
 BR 2001013628 A 20030701 (200356) C07D471-04
 CN 1451005 A 20031022 (200406) C07D471-04
 MX 2003001821 A1 20030601 (200417) A61K031-519
 JP 2004507541 W 20040311 (200419) 252 C07D471-04
 US 6753427 B2 20040622 (200445) A61K031-519
 US 2004192709 A1 20040930 (200465) A61K031-519
 ZA 2003001079 A 20040728 (200466) 138 C07D000-00
 US 6861423 B2 20050301 (200516) # A61K031-535

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2002018380	A1	WO 2001-EP9689	20010822	<--
US 2002055513	A1 Provisional	US 2000-229584P	20000831	<--
		US 2001-943338	20010830	<--
AU 2001093784	A	AU 2001-93784	20010822	<--
US 2002137756	A1 Provisional	US 2000-229584P	20000831	<--
		US 2001-943407	20010830	<--
US 6506749	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
		US 2001-943407	20010830	<--
US 6518276	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
		US 2001-943338	20010830	<--
EP 1315726	A1	EP 2001-974206	20010822	<--
		WO 2001-EP9689	20010822	<--
KR 2003022422	A	KR 2003-702936	20030227	
US 2003144307	A1 Div ex	US 2001-943338	20010830	<--
		US 2002-315633	20021210	<--
US 2003153586	A1 Cont of	US 2001-943407	20010830	<--
		US 2002-230723	20020829	<--
BR 2001013628	A	BR 2001-13628	20010822	<--
		WO 2001-EP9689	20010822	<--
CN 1451005	A	CN 2001-815030	20010822	<--
MX 2003001821	A1	WO 2001-EP9689	20010822	<--
		MX 2003-1821	20030228	
JP 2004507541	W	WO 2001-EP9689	20010822	<--
		JP 2002-523895	20010822	<--
US 6753427	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
	Div ex	US 2001-943338	20010830	<--
		US 2002-315633	20021210	<--
US 2004192709	A1 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
	Div ex	US 2001-943338	20010830	<--
	Div ex	US 2002-315633	20021210	<--
		US 2004-816554	20040401	
ZA 2003001079	A	ZA 2003-1079	20030207	
US 6861423	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
	Cont of	US 2001-943407	20010830	<--
		US 2002-230723	20020829	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001093784	A Based on	WO 2002018380
EP 1315726	A1 Based on	WO 2002018380
US 2003144307	A1 Div ex	US 6518276
US 2003153586	A1 Cont of	US 6506749
BR 2001013628	A Based on	WO 2002018380
MX 2003001821	A1 Based on	WO 2002018380
JP 2004507541	W Based on	WO 2002018380
US 6753427	B2 Div ex	US 6518276
US 2004192709	A1 Div ex	US 6518276
	Div ex	US 6753427
US 6861423	B2 Cont of	US 6506749

PRIORITY APPLN. INFO: US 2000-229584P

20000831; US
 2001-943338 20010830;
 US 2001-943407
 20010830; US
 2000-229577P 20000831;
 US 2002-315633
 20021210; US
 2002-230723 20020829;
 US 2004-816554 20040401

INT. PATENT CLASSIF.:

MAIN: A61K031-519; A61K031-535; C07D000-00; C07D471-04
 SECONDARY: A61K031-52; A61P001-04; A61P011-00; A61P011-06;
 A61P019-02; A61P025-28; A61P029-00; A61P031-00;
 A61P031-06; A61P037-06; A61P043-00; C07D221-00;
 C07D239-00; C07D487-02; C07D487-04
 INDEX: C07D221:00; C07D239:00; C07D471-04; C07D221:00;
 C07D239:00; C07D471-04

BASIC ABSTRACT:

WO 200218380 A UPAB: 20050316

NOVELTY - 7-Oxo-pyridopyrimidine derivatives (I) are new.

DETAILED DESCRIPTION - 7-Oxo-pyridopyrimidine derivatives of formula (I) and their salts and prodrugs are new.

R1 = H or alkyl;

R2 = substituted alkyl, optionally hetero substituted cycloalkyl, heteroalkyl substituted cycloalkyl, hetero substituted cycloalkyl-alkyl, heterocyclyl, heterocyclyl spirocycloalkyl, aralkoxy, alkoxy, -alkylene-S(O)_n-alkyl or SO₂Ar₂;

n = 1 or 2;

R3 = H, amino, monoalkylamino, dialkylamino, acylamino, -NRa-C(=O)-Rb, alkyl, cycloalkyl, aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, -alkylene-C(O)-R, acyl or phthalimidoalkyl;

Ra = H or alkyl;

Rb = heterocyclyl or heteroalkyl;

R = H, alkyl, hydroxy, alkoxy, amino, monoalkylamino or dialkylamino,

and

Ar₁, Ar₂ = aryl.

An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY - Antiarthritic; Antiinflammatory; Nootropic; Neuroprotective; Antirheumatic; Antigout; Osteopathic; Dermatological; Immunosuppressive; Antiasthmatic; Virucide; Antibacterial; Protozoacide; Immunomodulator; Anti-HIV; Vasotropic; Antiarteriosclerotic; Thrombolytic; Anticoagulant; Cardiant; Antidiabetic; Dermatological; Antipsoriatic; Vulnerary; Neuroleptic; Gastrointestinal; Antiulcer;

Ophthalmological; Cytostatic; Nephrotropic; Gynecological; Antipyretic.

MECHANISM OF ACTION - p38 Mitogen-activated protein kinase (MAP) inhibitor; LPS-induced tumor necrosis factor alpha (TNF- alpha) production inhibitor in THP1 cells; Cyclooxygenase-2 inhibitor.

In an assay measuring the transfer of the gamma -phosphate from gamma -33P-ATP by p-38 kinase to Myelin Basic Protein using a minor modification of the method described in Ahn, N. G; et al. J Biol. Chem Volume 266(7), 4220-4227, a compound of formula (Ia) exhibited an IC50 value of 3.00 multiply 10-10 M for inhibiting p38 enzyme.

USE - Used for treating arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease. (I) Are also used for treating fever, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, osteoarthritis, other arthritic conditions, pulmonary disorders and lung inflammation, including pulmonary sarcoidosis, asthma, silicosis, chronic pulmonary inflammatory disease, viral and bacterial infections including sepsis, septic shock, gram negative sepsis, malaria, meningitis secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), pneumonia and herpes virus.

(I) Are also used in the treatment of bone resorption disease, osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft versus host reaction and allograft rejections, cardiovascular diseases including atherosclerosis, thrombosis, congestive heart failure, cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, myalgias due to infection, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus, skin related conditions e.g. psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation, gastrointestinal conditions such as inflammatory bowel disease, gastritis and ulcerative colitis, ophthalmic diseases e.g. retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, angiogenesis including neoplasia, metastasis, ophthalmological conditions e.g. corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma, ulcerative diseases e.g. gastric ulcer, pathological, but non-malignant conditions e.g. hemangiomas including infantile hemangiomas, angiofibroma of the nasopharynx and a vascular necrosis of bone, diabetic nephropathy and cardiomyopathy, and disorders of the female reproductive system such as endometriosis.

(I) Are used for veterinary treatment of companion animals, exotic animals and farm animals.

Dwg.0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; GI; DCN
MANUAL CODES:	CPI: B06-D08; B14-A01; B14-A02; B14-A02A3; B14-A03B; B14-C03; B14-C04; B14-C09; B14-E08; B14-E10; B14-E10C; B14-F01B; B14-F04; B14-F05; B14-F07; B14-G01; B14-G01B; B14-H01; B14-J01A2; B14-J01A4; B14-K01; B14-K01A; B14-N01; B14-N03; B14-N10; B14-N12; B14-N14; B14-N16; B14-N17A; B14-N17B; B14-N17C; B14-S01; B14-S04; B14-S06

TECH UPTX: 20020528

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises contacting a pyridopyrimidine compound of formula (II) with an amine of formula R1R2NH.
n' = 0-2 (preferably 1 or 2), and

R6 = alkyl.

ABEX

UPTX: 20020528

SPECIFIC COMPOUNDS - 151 Compounds are disclosed e.g:

6-(2-chlorophenyl)-2-(4-hydroxy-cyclohexylamino)-8-methyl-8H-pyrido(2,3-d)pyrimidin-7-one (Ib).

ADMINISTRATION - The dosage is 0.1-100 (preferably 0.5-5) mg/kg/day enterally, orally, nasally, rectally or parenterally.

EXAMPLE - To a mixture of 4-methylamino-2-methylthiopyrimidine-5-carboxaldehyde (3.3 g), ethyl-2-chlorophenylacetate (4 g) in N-Methyl Pyrrolidone (30 ml) was added resin, polymer bound 1,3,4,6,7,8-hexahydro-2H-pyrimido(1,2-a)pyrimidine (1.5 g). After work up the sulfide (4 g) was obtained. A solution of sulfide in chloroform (13.5 g) was cooled in the ice and treated with 3-chloroperbenzoic acid (20.5 g). After work up 6-(2-chloro-cyclohexa-2,4-dienyl)-2-methanesulfonyl-2-methyl-8H-pyrido(2,3-d)pyrimidin-7-one (13.1 g) was obtained.

DEFINITIONS - Preferred Definitions:

Ar1 = 2-chlorophenyl, 2-fluorophenyl, 2-methylphenyl or 2-methoxyphenyl;

R3 = H, amino, dimethylamino, isopropylamino, (morpholinoformyl)amino, methyl, 2,2,2-trifluoroethyl, cyclopropyl, cyanomethyl, 2-hydroxyethyl, 4-fluorophenyl, benzyl, carboxymethyl or methoxycarbonylmethyl, ethyl, 2-fluoroethyl, 2-hydroxy-2-methylpropyl or 2-phthalimidopropyl (preferably H or methyl);

R1 = H or methyl;

R2 = hetero substituted cycloalkyl or heterocyclyl (preferably 4-hetero-substituted cyclohexyl or substituted piperidinyl, especially 4-hydroxy-cyclohexyl, N-methanesulfonyl-piperidin-4-yl or 4-tetrahydropyranyl) or alkylsulfonylalkyl (preferably(1,1-dimethyl-2-methylsulfonyl)ethyl or (1,1-dimethyl-3-methylsulfonyl)propyl).

L638 ANSWER 74 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-489654 [52] WPIX

CROSS REFERENCE: 2002-304240 [34]

DOC. NO. CPI: C2002-138941

TITLE: New 7-oxo-pyridopyrimidines or their prodrugs or salts useful in the treatment of p38 mediated disorders e.g. arthritis.

DERWENT CLASS: B02

INVENTOR(S): CHEN, J J; DUNN, J P; GOLDSTEIN, D M; LIM, J A; ARZENO, H B

PATENT ASSIGNEE(S): (HOFF) HOFFMANN LA ROCHE & CO AG F; (ARZE-I) ARZENO H B; (CHEN-I) CHEN J J; (DUNN-I) DUNN J P; (GOLD-I) GOLDSTEIN D M; (LIMJ-I) LIM J A; (SYNT) SYNTEX USA LLC

COUNTRY COUNT: 98

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002018379	A2	20020307	(200252)*	EN	64	C07D471-04<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO							
RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW							
AU 2002012147	A	20020313	(200252)			C07D471-04<--	
US 6506749	B2	20030114	(200313)			C07D471-04	
US 6518276	B2	20030211	(200314)			A61K031-519	

EP 1315727 A2 20030604 (200337) EN C07D471-04
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR
 KR 2003022423 A 20030315 (200350) C07D471-04
 US 2003144307 A1 20030731 (200354) # A61K031-519
 BR 2001013590 A 20030722 (200365) C07D471-04
 CN 1451004 A 20031022 (200406) C07D471-04
 MX 2003001733 A1 20030501 (200415) A61K031-519
 JP 2004507540 W 20040311 (200419) 125 C07D471-04
 US 6753427 B2 20040622 (200445) A61K031-519
 US 2004192709 A1 20040930 (200465) A61K031-519
 ZA 2003001078 A 20040728 (200466) 78 C07D000-00
 EP 1315727 B1 20050629 (200543) EN C07D471-04
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR
 DE 60111752 E 20050804 (200552) C07D471-04

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE	
WO 2002018379	A2	WO 2001-EP9688	20010822	<--
AU 2002012147	A	AU 2002-12147	20010822	<--
US 6506749	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
		US 2001-943407	20010830	<--
US 6518276	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
		US 2001-943338	20010830	<--
EP 1315727	A2	EP 2001-980258	20010822	<--
		WO 2001-EP9688	20010822	<--
KR 2003022423	A	KR 2003-702955	20030227	
US 2003144307	A1 Div ex	US 2001-943338	20010830	<--
		US 2002-315633	20021210	<--
BR 2001013590	A	BR 2001-13590	20010822	<--
		WO 2001-EP9688	20010822	<--
CN 1451004	A	CN 2001-815027	20010822	<--
MX 2003001733	A1	WO 2001-EP9688	20010822	<--
		MX 2003-1733	20030226	
JP 2004507540	W	WO 2001-EP9688	20010822	<--
		JP 2002-523894	20010822	<--
US 6753427	B2 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
	Div ex	US 2001-943338	20010830	<--
		US 2002-315633	20021210	<--
US 2004192709	A1 Provisional	US 2000-229577P	20000831	<--
	Provisional	US 2000-229584P	20000831	<--
	Div ex	US 2001-943338	20010830	<--
	Div ex	US 2002-315633	20021210	<--
		US 2004-816554	20040401	
ZA 2003001078	A	ZA 2003-1078	20030207	
EP 1315727	B1	EP 2001-980258	20010822	<--
		WO 2001-EP9688	20010822	<--
DE 60111752	E	DE 2001-00111752	20010822	<--
		EP 2001-980258	20010822	<--
		WO 2001-EP9688	20010822	<--

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2002012147	A Based on	WO 2002018379
EP 1315727	A2 Based on	WO 2002018379
US 2003144307	A1 Div ex	US 6518276
BR 2001013590	A Based on	WO 2002018379
MX 2003001733	A1 Based on	WO 2002018379
JP 2004507540	W Based on	WO 2002018379
US 6753427	B2 Div ex	US 6518276
US 2004192709	A1 Div ex	US 6518276
	Div ex	US 6753427
EP 1315727	B1 Based on	WO 2002018379
DE 60111752	E Based on	EP 1315727
	Based on	WO 2002018379

PRIORITY APPLN. INFO: US 2000-229577P
 20000831; US
 2000-229584P 20000831;
 US 2001-943407
 20010830; US
 2001-943338 20010830;
 US 2002-315633
 20021210; US 2004-816554
 20040401

INT. PATENT CLASSIF.:

MAIN: A61K031-519; C07D000-00; C07D471-04
 SECONDARY: A61P001-04; A61P001-16; A61P003-10; A61P007-02;
 A61P009-04; A61P009-10; A61P011-00; A61P011-06;
 A61P013-12; A61P015-08; A61P019-02; A61P019-06;
 A61P019-10; A61P025-00; A61P025-28; A61P027-02;
 A61P027-16; A61P029-00; A61P031-04; A61P031-06;
 A61P031-16; A61P031-18; A61P031-22; A61P033-06;
 A61P035-00; A61P035-04; A61P037-02; A61P037-06;
 C07D221-00; C07D239-00; C07D239-46; C07D487-02
 INDEX: C07D221:00; C07D239:00; C07D471-04; C07D221:00;
 C07D239:00; C07D471-04

BASIC ABSTRACT:

WO 200218379 A UPAB: 20050815
 NOVELTY - 7-Oxo-pyridopyrimidines (I) or their prodrugs or salts are new.
 DETAILED DESCRIPTION - 7-Oxo-pyridopyrimidines of formula (I) or
 their salts or prodrugs are new.
 R1 = H or alkyl;
 R2 = -CR'R''-Ra, Rx-S(O)2-Ry, alkoxy-substituted alkyl,
 heterocyclalkyl or 4-5C cycloalkyl;
 R' and R'' = H, hydroxyalkyl or alkyl;
 Ra = hydroxyalkyl;
 Rx = alkyl;
 Ry = alkenyl; or
 N(R1R2) = heterocyclalkyl;
 R3 = H, alkyl, amino, monoalkylamino, dialkylamino, cycloalkyl,
 aryl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, alkylene-C(O)-R or
 acyl;
 R = H, alkyl, hydroxy, alkoxy, amino, monoalkylamino or
 dialkylamino; and
 Ar1 = aryl
 with the proviso that the OH group in R2 can be in the form of an
 ester, carbamate, carbonate or a sulfonate derivative; and at least one of
 R' and R is alkyl or hydroxyalkyl.
 INDEPENDENT CLAIMS are also included for:
 (1) preparation of (I);
 (2) preparation of pyrimidine compound of formula (IIc) comprising:
 (a) contacting an acetal of formula NC-CH2-CH(ORa)2 with an alkyl

formate of formula HCO₂R in the presence of a condensation base to produce a condensed product; and

(b) contacting the condensed product with thiourea in the presence of a cyclization base to produce (IIc);

(3) preparation of pyridopyrimidine of formula (IIe) comprising either:

(i) contacting (IIc) with an alkylating agent of formula R-X₁ in the presence of an alkylating base to produce alkylating pyrimidine of formula (IIId); and

(ii) contacting (IIId) with an aryl acetate of formula Ar₁-CH₂-CO₂R (A) in the presence of a cyclization base to produce (IIe); or

(iii) contacting (IIc) with the aryl acetate of formula Ar₁-CH₂-CO₂R in the presence of a cyclization base to produce a thiol pyridopyrimidine of formula (III); and

(iv) contacting (III) with the alkylating agent of formula R-X₁ in the presence of alkylating base to produce to form (IIe);

(4) preparation of pyridopyrimidine of formula (Ie) comprising contacting (IIe) with a nitrogen alkylating agent of formula R₃-X₂;

(5) (IIc), (IIe) and (Ie); and

(6) use of (I) in the preparation of a medicament for the prevention or treatment of p38 mediated disorders.

R, R_a = alkyl;

X₁ = leaving group;

R₃' = alkyl, amino, mono- or di-alkylamino, cycloalkyl, aralkyl, haloalkyl, heteroalkyl, cyanoalkyl, alkylene-C(O)-R_t or alkyl;

R_t = H, alkyl, hydroxy, alkoxy, amino or mono- or di-alkylamino;

X₂ = leaving group.

ACTIVITY - Antiarthritic; Antiinflammatory; Nootropic; Neuroprotective; Antirheumatic; Antigout; Osteopathic; Dermatological; Immunosuppressive; Antiasthmatic; Antiviral; Antibacterial; Antiprotozoal; Antimalarial; Cerebroprotective; Immunomodulator; Anti-HIV; Vasotropic; Antiarteriosclerotic; Thrombolytic; Anticoagulant; Cardiant; Antidiabetic; Antipsoriatic; Vulnerary; Neuroleptic; Gastrointestinal; Antiulcer; Ophthalmological; Cytostatic; Nephrotropic; Gynecological; Cardiovascular; Respiratory; Antipyretic; Musculatropic; Antiallergic; Cholerectic; Analgesic; Endocrinal.

MECHANISM OF ACTION - p38 Mitogen-activated protein kinase (MAP) inhibitor; inhibitor of LPS-induced TNF- α production in THP1 cells; Antimetastatic; Protein kinase inhibitor; Cyclooxygenase-2 inhibitor.

The p-38 MAP kinase inhibitory activity of 6-(2-chloro-phenyl)-8-(4-fluoro-phenyl)-2-(2-hydroxy-1,2-dimethyl-propylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (Ia) was determined by the transfer of the gamma phosphate from gamma -33P-ATP by p-38 kinase to Myelin Basic Protein (MBP). (Ia) showed an IC₅₀ of 0.0003 micro M.

USE - In the manufacture of a medicament useful in the treatment of p38 mediated disorders e.g. arthritis, Crohn's disease, Alzheimer's disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease; as a therapeutic agents (all claimed). As anti-inflammatory agent, as antipyretic; in the treatment of fever, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, systemic lupus erythematosus, juvenile arthritis, osteoarthritis, other arthritic conditions; pulmonary disorders and lung inflammation, including pulmonary sarcoidosis, asthma, silicosis, chronic pulmonary inflammatory disease. In the treatment of viral and bacterial infections including sepsis, septic shock, gram negative sepsis, malaria, meningitis secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), ARC (AIDS related complex), pneumonia and herpes virus. Also in the treatment of bone resorption disease, osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury disease including graft versus host reaction and allograft rejections,

cardiovascular diseases including atherosclerosis, thrombosis, congestive heart failure, cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection; in the treatment of influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythematosus, skin related conditions e.g. psoriasis, eczema, burns, dermatitis, keloid formation and scar tissue formation. In the treatment of gastrointestinal conditions such as inflammatory bowel disease and ulcerative colitis; ophthalmic diseases e.g. retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, angiogenesis including neoplasia, metastasis; ophthalmological conditions e.g. corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases e.g. gastric ulcer, pathological, but non-malignant conditions e.g. hemangiomas including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis. For preventing the production of cyclooxygenase-2; for veterinary treatment of companion animals, exotic animals and farm animals; in co-therapies. Also useful in the treatment of immunological, oncological, bronchopulmonary, dermatological and cardiovascular disease.

ADVANTAGE - (I) exhibits effective activity against p38 in vivo. (I) exhibits protein kinase inhibitory activity.

Dwg.0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-D08; B06-H; B07-D12; B07-H; B11-C01C; B14-A01;
 B14-A01B2; B14-A02; B14-A02A3; B14-A02B2; B14-A03B;
 B14-C02; B14-C03; B14-C04; B14-C09; B14-C09A;
 B14-C09B; B14-D01B; B14-D05C; B14-D07C; B14-E08;
 B14-E10; B14-E10C; B14-F01; B14-F01B; B14-F02;
 B14-F02F1; B14-F04; B14-F05; B14-F07; B14-G01B;
 B14-G02C; B14-G03; B14-H01; B14-H01B; B14-J01A2;
 B14-J01A4; B14-J05; B14-K01; B14-K01A; B14-K01F;
 B14-N01; B14-N03; B14-N10; B14-N12;
 B14-N14; B14-N16; B14-N17; B14-N17A; B14-N17B;
 B14-N17C; B14-S01; B14-S04; B14-S06; B14-S12

TECH UPTX: 20020815

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Process (claimed): (I) is prepared by contacting a compound of formula (Ig) with an amine of formula R1R2NH to form (I).

n = 0 - 2 (preferably 1 or 2); and

R6 = alkyl.

Preferred Components: The condensation base is tert-butoxide and the cyclization base is an alkoxide.

ABEX UPTX: 20020815

SPECIFIC COMPOUNDS - 27 Compounds are specifically disclosed as (I) e.g. 6-(2-chloro-phenyl)-8-(4-fluoro-phenyl)-2-(2-hydroxy-1,2-dimethyl-propylamino)-8H-pyrido(2,3-d)pyrimidin-7-one of formula (Ia).

ADMINISTRATION - (I) is administered enterally, orally, nasally, rectally or parenterally in a daily dosage of 0.1 - 100 (preferably 0.5 - 5) mg/kg.

EXAMPLE - To a solution of 3-amino-2-methyl-butan-2-ol (0.28 g) in acetonitrile (4 ml) at room temperature (RT) was added trimethylsilyl cyanide (0.8 ml). The resulting mixture was heated to 80degreesC until the mixture became homogenous. Then 6-(2-chloro-phenyl)-8-(4-fluoro-phenyl)-2-methanesulfonyl-8H-pyrido(2,3-d)pyrimidin-7-one (0.4 g) was added to the reaction mixture and stirred at 80degreesC for 35 minutes. The mixture was cooled to RT and methanol (15 ml) was added and stirred for 5 minutes. The

mixture was concentrated at reduced pressure at 50degreesC. The residue was diluted with ethyl acetate (35 ml) and water (25 ml). After work up, 6-(2-chloro-phenyl)-8-(4-fluoro-phenyl)-2-(2-hydroxy-1,2-dimethyl-propylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (Ia) (219 mg) was obtained as off-white powder.

DEFINITIONS - Preferred Definitions:

Ar1 = optionally substituted phenyl, preferably phenyl substituted by one or two halo, alkyl or methoxy groups, particularly 2-chlorophenyl, 2-methylphenyl or 2-methoxyphenyl);

R1 = H or methyl;

R2 = (1,1-dimethyl-2-hydroxy)ethyl, (1,2-dimethyl-2-hydroxy)propyl or (1-substituted piperidin-4-yl)methyl); and

X1, X2 = halide.

L638 ANSWER 75 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-154926 [20] WPIX
 DOC. NO. CPI: C2002-048500
 TITLE: New composition for stimulating osteoblast production and for inducing local tissue formation from a progenitor cell, comprises an extract of bioactive glass.
 DERWENT CLASS: B04 B06 D16 D22 L01
 INVENTOR(S): BUTTERY, L D; HENCH, L L; MAROOTHYNADEN, J; POLAK, J M; XYNOS, I D; BUTTERY, L D K
 PATENT ASSIGNEE(S): (IMCO-N) IMPERIAL COLLEGE INNOVATIONS LTD; (BUTT-I) BUTTERY L D K; (HENC-I) HENCH L L; (MARO-I) MAROOTHYNADEN J; (POLA-I) POLAK J M; (XYNO-I) XYNOS I D
 COUNTRY COUNT: 97
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002004606	A1	20020117	(200220)*	EN	35	C12N005-00	<--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU							
SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW							
AU 2001080507	A	20020121	(200234)			C12N005-00	<--
EP 1311656	A1	20030521	(200334)	EN		C12N005-00	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI TR							
US 2004009598	A1	20040115	(200406)			C12N005-00	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002004606	A1	WO 2001-US21801	20010711 <--
AU 2001080507	A	AU 2001-80507	20010711 <--
EP 1311656	A1	EP 2001-958900	20010711 <--
		WO 2001-US21801	20010711 <--
US 2004009598	A1	WO 2001-US21801	20010711 <--
		US 2003-332731	20030707

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001080507 A Based on WO 2002004606
EP 1311656 A1 Based on WO 2002004606

PRIORITY APPLN. INFO: **US 2000-217460P**
 20000711; US 2003-332731
 20030707

INT. PATENT CLASSIF.:

MAIN: C12N005-00

SECONDARY: A01N063-00; C12N005-02

BASIC ABSTRACT:

WO 200204606 A UPAB: 20020402

NOVELTY - A composition comprising an extract of bioactive glass containing (weight%) SiO₂ (42 - 52), CaO (15 - 25), Na₂O (15 - 25) and P₂O₅ (1 - 9), where the extract of bioactive glass stimulates osteoblast proliferation, differentiation and/or function, is new..

ACTIVITY - Osteopathic; antiarthritic; antirheumatic; antipsoriatic; antiulcer; antiinflammatory; dermatological; immunosuppressive; antipyretic; hemostatic; **ophthalmologic**; cytostatic; vulnerary; antibacterial; periodontal. Test details are described but no results given.

MECHANISM OF ACTION - None given.

USE - The composition is used:

(i) for enhancing osteoblast production, by using devices e.g. prosthetic implants, sutures, stents, screws, plates, valves and tubes;
(ii) for stimulating osteoblast proliferation, differentiation and/or function;

(iii) for inducing local tissue formation from a progenitor cell in a mammal;

(iv) for accelerating allograft repair in a mammal;

(v) for promoting in vivo integration of an implantable prosthetic device to enhance the bond strength between the prosthesis and the existing target tissue at the joining site;

(vi) for treating osteoblast-related tissue degenerative conditions in a mammal;

(vii) for upregulating at least one gene e.g. CD44, **mitogen**-activated protein (MAP) **kinase** activated protein kinase 2, integrin beta 1, RCL growth-related c-myc responsive gene, insulin-like growth factor (IGF)-II, IGF binding protein (BP)3, matrix metalloproteinase (MMP)2, MMP14, metalloproteinase inhibitor 1 precursor (TIMP)1, TIMP2, procollagen a2, decorin, c-jun, c-myc, calpain and defender against cell death (DAD)1, involved in the proliferation, differentiation and/or function of osteoblasts;

(viii) for increasing IGF-II availability in cells and tissues (all claimed);

(ix) for repair and reconstruction of bone, cartilage and enhancement of healing of other tissues and in other surrounding nervous system-associated tissue for use in neural regeneration and repair;

(x) in cartilage repair following joint injury or in osteoarthritis treatment;

(xi) in treating certain congenital disease and developmental abnormalities of cartilage, bone and other tissues;

(xii) for treating heritable conditions including osteogenesis imperfecta, the Hurler and Marfan syndromes, several disorders of epiphyseal and metaphyseal growth centers in hypophosphatasia, a deficiency in alkaline phosphatase enzymatic activity, inflammatory joint diseases including infectious, non-infectious, rheumatoid and psoriatic arthritis, bursitis, ulcerative colitis, regional enteritis, Whipple's disease, ankylosing spondylitis, systematic lupus erythematosus (SLE), progressive systemic sclerosis (scleroderma), polymyositis (dermatomyositis), necrotizing vasculitides, **Sjogren's** syndrome

(sicca syndrome), rheumatic fever, amyloidosis, thrombotic thrombocytopenic purpura and relapsing polychondritis, and heritable disorders of connective tissue including homocystinuria, Ehlers-Danlos syndrome, alkaptonuria, pseudoxanthoma elasticum, cutis laxa and myositis ossificans progressiva; and

(xiii) for filling voids present in aneurysms, during root of canal operation and those formed surgically e.g. removal of spleen, ovary, gallbladder or tumor.

ADVANTAGE - The composition permits the physician to obtain predictable bone and/or cartilage formation and can be used to treat more efficiently and/or effectively injuries, anomalies and disorders including e.g. forming local bone in fractures, non-union fractures, fusions and bony voids created in tumor resections or these resulting from cysts etc. The ability to enhance cartilage-inducing activity by administering the composition can permit faster or more extensive tissue regeneration required after complicated bone transplantation procedures can occur more quickly and completely using the composition. The composition prevents bacterial infection until the tooth is ultimately filled during a root canal operation.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-E03B; B04-F02; B04-H06; B04-H06H; B05-A01B; B05-B02A3; B05-B02C; B11-C04A; B14-C03; B14-C04; B14-C08; B14-C09B; B14-E08; B14-F08; B14-G02; B14-H01; B14-N01; B14-N03; B14-N17; B14-N17B; B14-N17C; B14-S01; D05-H08; D05-H10; D09-C01; L01-A01B; L01-A04; L01-A07A

TECH UPTX: 20020402

TECHNOLOGY FOCUS - CERAMICS AND GLASS - Preferred Composition: The bioactive glass is in the form of matrices for cell culture, sols, gels, particles, fibers or noninterlinked particles of bioactive glass. The size range of the particles is less than 1200 (preferably 100 - 800, especially less than 90) microns as measured by scanning electron microscope (SEM) or laser light scattering techniques. The composition is incorporated into a matrix carrier material to provide controlled release of the extract composition or is dispersed in an implantable or extracorporeal biocompatible carrier material. The composition further comprises at least one therapeutic agent.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The therapeutic agent is a healing promotion agent, growth factor, antiinflammatory agent or topical anesthetic.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Composition: The bioactive glass preferably comprises (wt. %) SiO₂ (45), CaO (24.5), Na₂O (24.5) and P₂O₅ (6). The composition may comprise an aqueous solution containing (parts per million (ppm)) Si (1 - 100, preferably 3 - 30), Ca (10 - 150, preferably 60 - 100) and P (5 - 50, preferably 10 - 40).

TECHNOLOGY FOCUS - POLYMERS - The matrix carrier material is a hydrogel.

ABEX UPTX: 20020402

ADMINISTRATION - The composition is administered orally, parenterally, subcutaneously, intravenously, intralesionally or topically or by direct injection into a bony defect or an adjacent tissue locus, or as an implant.

EXAMPLE - The effect of the ionic dissolution products of Bioglass D45S5 (RTM) (bioactive glass ceramic material) on human primary osteoblasts in vitro was evaluated. Osteoblasts were isolated from trabecular bone of femoral heads taken during total hip arthroplasty using the method as

described in Bereford et al., Metabolism Bone dis. and Rel. Res., 5:229 - 234 (1984). Cultures were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with fetal bovine serum (FBS) (10 %), L-glutamine (2 mM), penicillin G (50 U/ml), streptomycin B (50 micrograms/ml) and amphotericin B (0.3 micrograms/ml) (complete medium) at 37 degrees Centigrade, in 95 % air humidity and 5 % carbon dioxide. A solution containing the ionic dissolution products of bioglass 45S5 (RTM) was prepared by incubating bioglass Bioglass D 45S5 (RTM) (1 g) particulate in DMEM (100 ml) for 24 hours at 37 degrees Centigrade. The particulates were filtered and the collected medium was supplemented for the complete medium. The elemental content of the solution was determined by ICP analysis. Analysis of the composition revealed an increase in the concentration of Ca and most notably Si in the solution containing the ionic dissolution products of Bioglass D 45S5 (RTM).

L638 ANSWER 76 OF 94 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2000-611619 [58] WPIX
 DOC. NO. CPI: C2000-183052
 TITLE: New amino-thio-acrylonitrile derivatives, useful for treatment of e.g. arthritis, psoriasis, alcoholism and tumors, are **mitogen** activated protein kinase homolog inhibitors.
 DERWENT CLASS: B05
 INVENTOR(S): HOBBS, F W
 PATENT ASSIGNEE(S): (DUPO) DU PONT PHARM CO; (BRIM) BRISTOL-MYERS SQUIBB PHARMA CO; (HOBBS-I) HOBBS F W
 COUNTRY COUNT: 46
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2000056706	A1	20000928	(200058)*	EN	80	C07C323-60<--	
RW: AT BE CH CY DE DK EA ES FI FR GB GR IE IT LU MC NL PT SE							
W: AU BR CA CN CZ EE HU IL IN JP KR LT LV MX NO NZ PL RO SG SI SK TR							
UA VN ZA							
AU 2000037614	A	20001009	(200103)			C07C323-60<--	
EP 1163215	A1	20011219	(200206)	EN		C07C323-60<--	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC NL PT RO SE							
SI							
US 6703420	B1	20040309	(200418)			A61K031-275	
US 2004087583	A1	20040506	(200430)			C07D279-12	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000056706	A1	WO 2000-US7262	20000315 <--
AU 2000037614	A	AU 2000-37614	20000315 <--
EP 1163215	A1	EP 2000-916525	20000315 <--
		WO 2000-US7262	20000315 <--
US 6703420	B1 Provisional	US 1999-125330P	19990319 <--
		US 2000-527335	20000317 <--
US 2004087583	A1 Provisional	US 1999-125330P	19990319 <--
	Div ex	US 2000-527335	20000317 <--
		US 2003-697531	20031030

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2000037614	A Based on	WO 2000056706
EP 1163215	A1 Based on	WO 2000056706
US 2004087583	A1 Div ex	US 6703420

PRIORITY APPLN. INFO: **US 1999-125330P**
19990319; US
2000-527335 **20000317;**
US 2003-697531 **20031030**

INT. PATENT CLASSIF.:

MAIN: A61K031-275; C07C323-60; C07D279-12
SECONDARY: A61K031-277; A61K031-341; A61K031-381; A61K031-40;
A61K031-44; A61K031-445; A61K031-535; A61K031-54;
A61P035-00; C07C255-00; C07D207-32; C07D211-26;
C07D213-57; C07D265-30; C07D307-54; C07D333-24;
C07D333-34

BASIC ABSTRACT:

WO 200056706 A UPAB: 20040310

NOVELTY - New amino-thio-acrylonitrile derivatives.

DETAILED DESCRIPTION - Amino-thio-acrylonitrile derivatives (I) of formula (Ia) and (Ib) or their stereoisomers and salts are new.

R1 = phenyl, naphthyl, 2,3-dihydroindol-5-yl or 5-6 membered heteroaryl containing 1-4 O, N and/or S (each optionally substituted by 1-2 Ra);

Ra = H, F, Cl, Br, I, 1-4C alkyl, 1-4C alkoxy, OH, CH₂OH, NH₂, mono- or di-1-3C alkylamino, (H₂NCH₂C(O))NH, (H₂NCH(CH₃)C(O))NH, (CH₃NHCH₂C(O))NH, ((CH₃)₂NCH₂C(O))NH, CF₃, OCF₃, CN, NO₂, C(O)NH₂ or CH₃C(O)NH;Y' = phenyl or naphthyl (both optionally substituted by 1-5 Rb) or CHR₃;Rb = H, Cl, F, Br, I, 1-4C alkyl, OH, 1-4C alkoxy, CH₂OH, CH(OH)CH₃, CF₃, OCF₃, CN, NO₂, NH₂, mono- or di-1-3C alkylamino or COO-1-4C alkoxy;R2 = H, R2a, COR2a, CH(OH)R2a, CH₂R2a, OR2a, SR2a or NHR2a;

R2a = phenyl, naphthyl or 5-6 membered heteroaryl containing 1-4 O, N and/or S (optionally substituted by 1-5 Rb); and

R3 = phenyl or naphthyl (both optionally substituted by 1-2 Rb).

ACTIVITY - Antirheumatic; antiarthritic; osteopathic; antiinflammatory; **ophthalmological**; antiulcer; cytostatic; neuroprotective; antipsoriatic; antipyretic; cardiant; hemostatic; anticoagulant; thrombolytic; immunomodulator; antialcoholic; antibacterial; immunosuppressive; anti-HIV (human immunodeficiency virus).MECHANISM OF ACTION - MEK inhibitor. MEK is undefined, but is stated to be a homolog of **mitogen** activated protein **kinase** (MAPK)). Assays are described, but no results given.USE - (I) are used in the treatment of disorders related to MEK (not defined but stated to be a homolog of **mitogen** activated protein **kinase** (MAPK), especially rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, **corneal** ulceration, solid tumor growth, tumor invasion by secondary metastasis, neovascular glaucoma, , multiple sclerosis, psoriasis, fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease or human immunodeficiency virus (HIV) (all claimed). They are also useful as radiosensitizing agents against cancer and other proliferative diseases.

Dwg.0/0

FILE SEGMENT:	CPI
FIELD AVAILABILITY:	AB; GI; DCN
MANUAL CODES:	CPI: B06-D01; B07-H; B10-A15; B14-A01; B14-C04; B14-C09; B14-E11; B14-E12; B14-F01; B14-F04; B14-F08; B14-G01B; B14-G02C; B14-G02D; B14-H01; B14-M01A;

B14-N03; B14-N06B; B14-N17C; B14-S01;
B14-S06

TECH UPTX: 20001114

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by reacting a thiol of formula R1SH (II) with a malononitrile derivative of formula (III).

ABEX UPTX: 20001114

SPECIFIC COMPOUNDS - 92 Compounds (I) are specifically claimed e.g. E- and Z-alpha-(amino((2-aminophenyl)thio)methylene)-4-chloro-2-methyl-beta-phenylbenzenepropanenitrile.

ADMINISTRATION - Administration is oral, intravenous, intraperitoneal, subcutaneous, intramuscular, intranasal or transdermal. Oral dosage is 0.001-1000 (especially 1-20) mg/kg/day.

EXAMPLE - A solution of 2-methylbenzaldehyde (9.6 ml), malononitrile (5.5 g) and 3.5 M ammonium acetate in acetic acid (2.4 ml) in isopropanol (83 ml) was stirred overnight at room temperature. A precipitate formed, which was worked up to give 12.7 g 2-(2-methylbenzylidene)malononitrile. 4-Chlorophenyl magnesium bromide (2.1 ml; 1 M solution in ether) was added dropwise to a solution of the above product (0.32 g) in tetrahydrofuran (THF) (7.45 ml) at 0 degreesC, the mixture stirred for 1 hour, then worked up to give 0.25 g 2-(alpha-(2-methylphenyl)-4-chlorobenzyl)malononitrile. A solution of this product (0.2 g), 2-aminothiophenol (0.11 ml) and triethylamine (0.14 ml) in tetrahydrofuran (1.4 ml) was stirred under N2 for 78 hours, then absorbed onto silica gel and eluted with ethyl acetate to give 253 mg E- and Z-alpha-(amino((2-aminophenyl)thio)methylene)-4-chloro-2-methyl-beta-phenylbenzenepropanenitrile (m.pt. 63.5-72 degreesC; 6:4 ratio E:Z isomers).

=> d ibib ed ab hitind 77-

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 18 ANSWERS - CONTINUE? Y/(N):y

L638 ANSWER 77 OF 94 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001667629 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11571295
TITLE: Regulation of vascular endothelial growth factor expression by advanced glycation end products.
AUTHOR: Treins C; Giorgetti-Peraldi S; Murdaca J; Van Obberghen E
CORPORATE SOURCE: INSERM U145, IFR 50, Faculte de Medecine, Avenue de Valombrose, Nice 06107, Cedex 2, France.
SOURCE: Journal of biological chemistry, (2001 Nov 23) 276 (47) 43836-41. Electronic Publication: 2001-09-24. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011120
Last Updated on STN: 20030105
Entered Medline: 20011220
ED Entered STN: 20011120
Last Updated on STN: 20030105
Entered Medline: 20011220

AB Advanced glycation end products (AGEs) are generated during long term diabetes and are correlated with the development of diabetic complications, such as retinopathy. Diabetic retinopathy is characterized by an increased retinal neovascularization due to the action of the angiogenic factor, vascular endothelial growth factor (VEGF). In this report, we show that injection of insulin and glycated albumin (Alb-AGE) to mice increases VEGF mRNA expression in **eyes**. Insulin and Alb-AGE stimulate VEGF mRNA and protein expression in retinal epithelial cells (ARPE-19). Alb-AGE-induced VEGF expression is not modulated by the use of antioxidants, N-acetyl-L-cysteine or pyrrolidinedithiocarbamate, or by an inhibitor of phosphatidylinositol 3-kinase (PI3K), wortmannin. However, using an inhibitor of ERK activation, U0126, we show that Alb-AGE stimulates VEGF expression through an ERK-dependent pathway. Accordingly, we found that Alb-AGE activated mitogen-activate protein kinase, ERK1/2, JNK1/2, but not p38, and that Alb-AGE did not activate PI3K and PKB. Moreover, Alb-AGE activated the transcription factor, hypoxia inducible factor-1 (HIF-1) DNA binding activity. This activation is mediated by an increase in accumulation of the HIF-1alpha protein through an ERK-dependent pathway. Thus, stimulation of VEGF expression by Alb-AGE, through the activation of HIF-1, could play an important role in the development of diabetic retinopathy.

CT Check Tags: Male

1-Phosphatidylinositol 3-Kinase: ME, metabolism

Albumins: PH, physiology

Animals

Base Sequence

Cell Line

DNA Primers

*Endothelial Growth Factors: GE, genetics

Endothelial Growth Factors: ME, metabolism

Enzyme Activation

Epithelial Cells: ME, metabolism

*Gene Expression Regulation: PH, physiology

*Glycosylation End Products, Advanced: PH, physiology

*Lymphokines: GE, genetics

Lymphokines: ME, metabolism

Mice

Mitogen-Activated Protein Kinases: ME, metabolism

*Protein-Serine-Threonine Kinases

Proto-Oncogene Proteins: ME, metabolism

RNA, Messenger: GE, genetics

Research Support, Non-U.S. Gov't

Retina: CY, cytology

Retina: ME, metabolism

Signal Transduction

Transcription Factors: ME, metabolism

Vascular Endothelial Growth Factor A

Vascular Endothelial Growth Factors

CN 0 (Albumins); 0 (DNA Primers); 0 (Endothelial Growth Factors); 0 (Glycosylation End Products, Advanced); 0 (Lymphokines); 0 (Proto-Oncogene Proteins); 0 (RNA, Messenger); 0 (Transcription Factors); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors); 0 (hypoxia-inducible factor 1, alpha subunit); EC 2.7.1.137 (1-Phosphatidylinositol 3-Kinase); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Protein-Serine-Threonine Kinases); EC 2.7.1.37 (proto-oncogene proteins c-akt)

L638 ANSWER 78 OF 94 MEDLINE on STN

DUPLICATE 9

ACCESSION NUMBER: 2001484774 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11527089

TITLE: Modulation of retinal endothelial cell behaviour by insulin-like growth factor I and somatostatin analogues: implications for diabetic retinopathy.

AUTHOR: Wilson S H; Davis M I; Caballero S; Grant M B

CORPORATE SOURCE: University of Florida, Gainesville, USA.

SOURCE: Growth hormone & IGF research : official journal of the Growth Hormone Research Society and the International IGF Research Society, (2001 Jun) 11 Suppl A S53-9.
Journal code: 9814320. ISSN: 1096-6374.

PUB. COUNTRY: Scotland: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200201

ENTRY DATE: Entered STN: 20010903
Last Updated on STN: 20020129
Entered Medline: 20020128

ED Entered STN: 20010903
Last Updated on STN: 20020129
Entered Medline: 20020128

AB Evidence suggests the involvement of growth hormone (GH), insulin-like growth factor I (IGF-I) and somatostatin in the pathology associated with diabetic retinopathy. We examined the effect of IGF-I on human retinal endothelial cell (HREC) survival following high glucose exposure and serum starvation, examined the signalling pathways mediating the protective effect of IGF-I on HREC, and characterized somatostatin receptor-induced retinal endothelial cell death. IGF-I (10 ng/ml) protected HREC from apoptosis induced by high glucose and serum starvation. Wortmannin, a specific inhibitor of phosphatidylinositol-3-kinase, blocks the ability of IGF-I to protect HREC from apoptosis. Incubation of HREC in serum-free medium caused a time-dependent increase in c-Jun N-terminal kinase (JNK) activity, and continuous culture of HREC in the presence of IGF-I or vascular endothelial growth factor (VEGF) prevented JNK activation and arrested apoptosis. Activation of tyrosine kinase receptors results in extracellular signal-related kinase (ERK) activation and activation of ERK is required for proliferation. Both IGF-I and VEGF produced a time- and concentration-dependent increase in the activation of ERK. Type 2 and type 3 somatostatin receptors have been implicated in cell-cycle arrest and apoptosis. Activation of the type 3 receptor in HREC resulted in cell death. These studies suggest that IGF-I is critical for HREC survival, and that somatostatin analogues acting through the type 3 receptor have direct effects on retinal endothelial cells. Furthermore, it appears that the therapeutic efficacy of somatostatin analogues lies not only in systemic inhibition of GH, but also in modulating local growth factor effects.

CT Amides: PD, pharmacology
Apoptosis: DE, drug effects
Cell Survival: DE, drug effects
Cells, Cultured
Culture Media, Serum-Free
Diabetic Retinopathy: PP, physiopathology
Dose-Response Relationship, Drug
Endothelial Growth Factors: PD, pharmacology
 Endothelium, Corneal: CY, cytology
 *Endothelium, Corneal: DE, drug effects
 *Endothelium, Corneal: ME, metabolism
Glucose: PD, pharmacology
Humans
Indoles: PD, pharmacology

*Insulin-Like Growth Factor I: PD, pharmacology
 JNK Mitogen-Activated Protein Kinases
 Lymphokines: PD, pharmacology
 Mitogen-Activated Protein Kinase 1: DE, drug effects
 Mitogen-Activated Protein Kinase 1: ME, metabolism
 Mitogen-Activated Protein Kinase 3
 Mitogen-Activated Protein Kinases: DE, drug effects
 Mitogen-Activated Protein Kinases: ME, metabolism
 Phosphorylation
 Receptors, Somatostatin: AG, agonists
 Receptors, Somatostatin: ME, metabolism
 Signal Transduction
 Somatostatin: AG, agonists

*Somatostatin: PD, pharmacology
 Vascular Endothelial Growth Factor A
 Vascular Endothelial Growth Factors

RN 50-99-7 (Glucose); 51110-01-1 (Somatostatin); 67763-96-6 (Insulin-Like Growth Factor I)
 CN 0 (Amides); 0 (Culture Media, Serum-Free); 0 (Endothelial Growth Factors); 0 (Indoles); 0 (L 779976); 0 (Lymphokines); 0 (Receptors, Somatostatin); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors); 0 (somatostatin receptor 2); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 1); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 3); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L638 ANSWER 79 OF 94 MEDLINE on STN DUPLICATE 12
 ACCESSION NUMBER: 1999309054 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10340964
 TITLE: Expression of mitogen activated protein kinases in labial salivary glands of patients with Sjogren's syndrome.
 AUTHOR: Nakamura H; Kawakami A; Yamasaki S; Kawabe Y; Nakamura T; Eguchi K
 CORPORATE SOURCE: First Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan.
 SOURCE: Annals of the rheumatic diseases, (1999 Jun) 58 (6) 382-5.
 Journal code: 0372355. ISSN: 0003-4967.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199909
 ENTRY DATE: Entered STN: 19991005
 Last Updated on STN: 19991005
 Entered Medline: 19990922
 ED Entered STN: 19991005
 Last Updated on STN: 19991005
 Entered Medline: 19990922
 AB OBJECTIVE: The expression of CD40 and CD40 ligand (CD40L) in mononuclear cells (MNCs) infiltrating the salivary glands of patients with Sjogren's syndrome (SS) has recently been reported. This study determined the expression of mitogen activated protein kinase (MAP kinase) superfamilies, which act as downstream effector molecules of CD40, in MNCs infiltrating labial salivary tissues in SS patients. METHODS: Six HTLV-I seronegative SS patients and 10 HTLV-I seropositive patients including five HTLV-I associated myelopathy (HAM) patients were examined. The expression of MAP kinase superfamilies in labial salivary glands was examined by immunohistochemistry containing the mirror section technique.

RESULTS: Both active forms of **c-Jun N-terminal kinase** (JNK) and p38 were found in salivary infiltrating MNCs of SS patients. Only minimal expression of the active form of extracellular signal regulated kinase (ERK) was observed in these tissues, however, co-expression of active JNK and active p38 was confirmed by the mirror section technique. Furthermore, these protein kinases were co-expressed in CD40(+) MNCs. No difference in expression levels of active JNK and p38 was found in patients who were positive or negative for anti-HTLV-I antibody. CONCLUSION: These results indicate that JNK and p38, but not ERK, function as downstream effector molecules of CD40 in salivary infiltrating MNCs in SS patients, and suggest that these molecules may be involved in the pathological process of chronic sialadenitis in SS.

CT Check Tags: Female

Adult

Aged

Aged, 80 and over

Antigens, CD40: AN, analysis

*Ca(2+)-Calmodulin Dependent Protein Kinase: AN, analysis

HTLV-I Infections: EN, enzymology

Human T-lymphotropic virus 1

Humans

Immunohistochemistry

JNK Mitogen-Activated Protein Kinases

Lip

Middle Aged

*Mitogen-Activated Protein Kinases

Nuclear Proteins: AN, analysis

Research Support, Non-U.S. Gov't

*Salivary Glands: EN, enzymology

*Sjogren's Syndrome: EN, enzymology

CN 0 (Antigens, CD40); 0 (Nuclear Proteins); 0 (Pa2g4 protein, mouse); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L638 ANSWER 80 OF 94 MEDLINE on STN

ACCESSION NUMBER: 2001352148 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11416124

TITLE: Phosphorylation of MafA is essential for its transcriptional and biological properties.

AUTHOR: Benkhelifa S; Provot S; Nabais E; Eychene A; Calothy G; Felder-Schmittbuhl M P

CORPORATE SOURCE: UMR 146 CNRS-Institut Curie, Centre Universitaire, 91405 Orsay cedex, France.

SOURCE: Molecular and cellular biology, (2001 Jul) 21 (14) 4441-52.

Journal code: 8109087. ISSN: 0270-7306.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200107

ENTRY DATE: Entered STN: 20010730

Last Updated on STN: 20010730

Entered Medline: 20010726

ED Entered STN: 20010730

Last Updated on STN: 20010730

Entered Medline: 20010726

AB We previously described the identification of quail MafA, a novel

transcription factor of the Maf bZIP (basic region leucine zipper) family, expressed in the differentiating neuroretina (NR). In the present study, we provide the first evidence that MafA is phosphorylated and that its biological properties strongly rely upon phosphorylation of serines 14 and 65, two residues located in the transcriptional activating domain within a consensus for phosphorylation by mitogen-activated protein kinases and which are conserved among Maf proteins. These residues are phosphorylated by ERK2 but not by p38, JNK, and ERK5 in vitro. However, the contribution of the MEK/ERK pathway to MafA phosphorylation in vivo appears to be moderate, implicating another kinase. The integrity of serine 14 and serine 65 residues is required for transcriptional activity, since their mutation into alanine severely impairs MafA capacity to activate transcription. Furthermore, we show that the MafA S14A/S65A mutant displays reduced capacity to induce expression of QR1, an NR-specific target of Maf proteins. Likewise, the integrity of serines 14 and 65 is essential for the MafA ability to stimulate expression of crystallin genes in NR cells and to induce NR-to-lens transdifferentiation. Thus, the MafA capacity to induce differentiation programs is dependent on its phosphorylation.

CT Amino Acid Sequence
Animals
Binding Sites
 Eye Proteins: GE, genetics
Glycoproteins: GE, genetics
Hela Cells
Humans
Lens, Crystalline
*Leucine Zippers
*Mitogen-Activated Protein Kinase 1: ME, metabolism
Mitogen-Activated Protein Kinase 3
Mitogen-Activated Protein Kinase 7
 Mitogen-Activated Protein Kinase 8
Mitogen-Activated Protein Kinases: ME, metabolism
Molecular Sequence Data
Phosphoproteins: GE, genetics
Phosphoproteins: ME, metabolism
Phosphorylation
Proto-Oncogene Proteins: GE, genetics
*Proto-Oncogene Proteins: ME, metabolism
Proto-Oncogene Proteins: PH, physiology
Rabbits
Research Support, Non-U.S. Gov't
Serine: GE, genetics
Serine: ME, metabolism
Trans-Activators: GE, genetics
*Trans-Activators: ME, metabolism
Trans-Activators: PH, physiology
Transcription, Genetic
p38 Mitogen-Activated Protein Kinases
RN 56-45-1 (Serine)
CN 0 (**Eye Proteins**); 0 (Glycoproteins); 0 (KLRG1 protein, human); 0 (MAFA protein, human); 0 (Phosphoproteins); 0 (Proto-Oncogene Proteins); 0 (QR1 protein, Coturnix japonica); 0 (Trans-Activators); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 1); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 3); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 7); EC 2.7.1.37 (**Mitogen-Activated Protein Kinase 8**); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases)

L638 ANSWER 81 OF 94

MEDLINE on STN

ACCESSION NUMBER: 2000307877 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 10848599
 TITLE: The Ste20 kinase misshapen regulates both photoreceptor axon targeting and dorsal closure, acting downstream of distinct signals.
 AUTHOR: Su Y C; Maurel-Zaffran C; Treisman J E; Skolnik E Y
 CORPORATE SOURCE: Department of Pharmacology, Skirball Institute of Biomolecular Medicine, New York University Medical Center, New York, NY 10016, USA.
 SOURCE: Molecular and cellular biology, (2000 Jul) 20 (13) 4736-44.
 Journal code: 8109087. ISSN: 0270-7306.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200007
 ENTRY DATE: Entered STN: 20000728
 Last Updated on STN: 20020420
 Entered Medline: 20000720
 ED Entered STN: 20000728
 Last Updated on STN: 20020420
 Entered Medline: 20000720
 AB We have previously shown that the Ste20 kinase encoded by misshapen (msn) functions upstream of the c-Jun N-terminal kinase (JNK) mitogen-activated protein kinase module in Drosophila. msn is required to activate the Drosophila JNK, Basket (Bsk), to promote dorsal closure of the embryo. A mammalian homolog of Msn, Nck interacting kinase, interacts with the SH3 domains of the SH2-SH3 adapter protein Nck. We now show that Msn likewise interacts with Dreadlocks (Dock), the Drosophila homolog of Nck. dock is required for the correct targeting of photoreceptor axons. We have performed a structure-function analysis of Msn in vivo in Drosophila in order to elucidate the mechanism whereby Msn regulates JNK and to determine whether msn, like dock, is required for the correct targeting of photoreceptor axons. We show that Msn requires both a functional kinase and a C-terminal regulatory domain to activate JNK in vivo in Drosophila. A mutation in a PXXP motif on Msn that prevents it from binding to the SH3 domains of Dock does not affect its ability to rescue the dorsal closure defect in msn embryos, suggesting that Dock is not an upstream regulator of msn in dorsal closure. Larvae with only this mutated form of Msn show a marked disruption in photoreceptor axon targeting, implicating an SH3 domain protein in this process; however, an activated form of Msn is not sufficient to rescue the dock mutant phenotype. Mosaic analysis reveals that msn expression is required in photoreceptors in order for their axons to project correctly. The data presented here genetically link msn to two distinct biological events, dorsal closure and photoreceptor axon pathfinding, and thus provide the first evidence that Ste20 kinases of the germinal center kinase family play a role in axonal pathfinding. The ability of Msn to interact with distinct classes of adapter molecules in dorsal closure and photoreceptor axon pathfinding may provide the flexibility that allows it to link to distinct upstream signaling systems.
 CT Amino Acid Motifs
 Animals
 *Axons: ME, metabolism
 Drosophila: EM, embryology
 *Drosophila Proteins
 Embryo, Nonmammalian
 Eye: EM, embryology
 Eye: IR, innervation

Eye: ME, metabolism

Ganglia, Invertebrate: EM, embryology
 Ganglia, Invertebrate: ME, metabolism
 JNK Mitogen-Activated Protein Kinases
 Mitogen-Activated Protein Kinases: GE, genetics
 Mitogen-Activated Protein Kinases: ME, metabolism
 Nerve Tissue Proteins: GE, genetics
 Nerve Tissue Proteins: ME, metabolism

*Photoreceptors, Invertebrate: ME, metabolism

Proline

Protein-Serine-Threonine Kinases: GE, genetics

*Protein-Serine-Threonine Kinases: ME, metabolism

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Signal Transduction

Structure-Activity Relationship

src Homology Domains

RN 147-85-3 (Proline)

CN 0 (Drosophila Proteins); 0 (Nerve Tissue Proteins); 0 (dreadlocks protein, Drosophila); EC 2.7.1.- (Pak protein, Drosophila); EC 2.7.1.- (misshapen protein, Drosophila); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Protein-Serine-Threonine Kinases)

L638 ANSWER 82 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2003:155166 BIOSIS

DOCUMENT NUMBER: PREV200300155166

TITLE: Mechanisms of Proinflammatory Cytokines-Induced Inhibition of **Lacrimal** Gland Secretion.

AUTHOR(S): Byon, D. [Reprint Author]; Kublin, C. L. [Reprint Author]; Zoukhri, D. [Reprint Author]

CORPORATE SOURCE: Schepens Eye Research Institute, Boston, MA, USA

SOURCE: ARVO Annual Meeting Abstract Search and Program Planner, (2002) Vol. 2002, pp. Abstract No. 3144. cd-rom. Meeting Info.: Annual Meeting of the Association For Research in Vision and Ophthalmology. Fort Lauderdale, Florida, USA. May 05-10, 2002.

DOCUMENT TYPE: Conference; (Meeting)

Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 26 Mar 2003

Last Updated on STN: 26 Mar 2003

ED Entered STN: 26 Mar 2003

Last Updated on STN: 26 Mar 2003

AB Purpose: To investigate the role of the stress-activated protein kinase Jun NH2-terminal kinase (**JNK1/2**), the mitogen-activated protein kinase (MAPK also known as p42/44 ERK) and the constitutive and inducible nitric oxide synthases (cNOS and iNOS) in proinflammatory-induced inhibition of **lacrimal** gland secretion. Method: Recombinant human (rh) IL-1alpha, rhIL-1beta (1 mug each), lipopolysaccharide (LPS, 25 mug) or saline (vehicle) were injected (2 mul) into the **lacrimal** glands of anesthetized female BALB/c mice. Twenty-four hours later, **lacrimal** glands were removed and lobules were prepared. Lobules from the same animal were divided in half and used to measure peroxidase secretion or homogenized for western blotting analyses. For peroxidase secretion, lobules were stimulated for 20 min with high KCl (75 mM, to stimulate **lacrimal** gland nerve endings). For western blotting, the membranes were blotted either with antibodies against phosphorylated (activated) or total **JNK1/2** and p42/44 ERK (to normalize for

equal loading of the gels) and with antibodies against cNOS and iNOS. Results: KCl-induced peroxidase secretion was inhibited 65%, 64%, and 78% by rhIL-1alpha, rhIL-1beta and LPS, respectively. Compared to saline injected animals, cytokines or LPS treatment resulted in a 2- to 4-fold increase in JNK and ERK activity. Furthermore, whereas iNOS protein was not detected in saline-injected animals, this protein was induced after cytokine and LPS injection. In contrast, the amount of cNOS was not affected by either cytokine or LPS treatment. Conclusion: Our results show that, concomitant with cytokine or LPS-induced inhibition of neurally stimulated lacrimal gland secretion, there is increased expression of iNOS, probably through activation of JNK and/or ERK. These results suggest that inflammation-induced expression of iNOS and production of nitric oxide might be responsible for the impaired secretory function of the lacrimal gland associated with autoimmune xerophthalmia.

- CC General biology - Symposia, transactions and proceedings 00520
 - Cytology - Animal 02506
 - Cytology - Human 02508
 - Biochemistry studies - General 10060
 - Biochemistry studies - Proteins, peptides and amino acids 10064
 - Biochemistry studies - Lipids 10066
 - Biochemistry studies - Carbohydrates 10068
 - Biophysics - Membrane phenomena 10508
 - Enzymes - General and comparative studies: coenzymes 10802
 - Endocrine - General 17002
 - Sense organs - Physiology and biochemistry 20004
 - Sense organs - Pathology 20006
 - Nervous system - Physiology and biochemistry 20504
 - Immunology - General and methods 34502
 - Immunology - Immunopathology, tissue immunology 34508
- IT Major Concepts
 - Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Sense Organs (Sensory Reception)
- IT Parts, Structures, & Systems of Organisms
 - lacrimal gland: sensory system, secretory function; membranes; nerve endings: nervous system
- IT Diseases
 - autoimmune xerophthalmia: eye disease, immune system disease
- IT Diseases
 - inflammation: immune system disease
 - Inflammation (MeSH)
- IT Chemicals & Biochemicals
 - ERK [extracellular signal-regulated kinase]; IL-1-alpha [interleukin-1-alpha]: recombinant; IL-1-beta [interleukin-1-beta]: recombinant; Jun amino-terminal kinase 1 [JNK1]: stress-activated protein kinase, phosphorylation; Jun amino-terminal kinase 2 [JNK2]: stress-activated protein kinase, phosphorylation; antibodies; constitutive nitric oxide synthase [cNOS] [EC 1.14.13.39]; inducible nitric oxide synthase [iNOS] [EC 1.14.13.39]: expression; lipopolysaccharide [LPS]: recombinant; mitogen-activated protein kinase [MAPK, p42/44 ERK] [EC 2.7.1.37]: phosphorylation; nitric oxide; peroxidase [EC 1.11.1.7]: secretion; potassium chloride; proinflammatory cytokines
- IT Methods & Equipment
 - Western blotting analysis: genetic techniques, laboratory techniques
- ORGN Classifier
 - Hominidae 86215
 - Super Taxa

Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human (common)
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
 ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 mouse (common): animal model, strain-BALB/c, female
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
 Rodents, Vertebrates
 RN 142243-02-5 (ERK)
 142243-02-5 (extracellular signal-regulated kinase)
 125978-95-2 (constitutive nitric oxide synthase)
 125978-95-2 (cNOS)
 125978-95-2 (EC 1.14.13.39)
 501433-35-8 (inducible nitric oxide synthase)
 125978-95-2 (inducible nitric oxide synthase)
 501433-35-8 (iNOS)
 125978-95-2 (iNOS)
 501433-35-8 (EC 1.14.13.39)
 125978-95-2 (EC 1.14.13.39)
 142243-02-5 (mitogen-activated protein kinase)
 9026-43-1 (mitogen-activated protein kinase)
 142243-02-5 (MAPK)
 9026-43-1 (MAPK)
 142243-02-5 (p42/44 ERK)
 9026-43-1 (p42/44 ERK)
 142243-02-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)
 10102-43-9 (nitric oxide)
 9003-99-0 (peroxidase)
 9003-99-0 (EC 1.11.1.7)
 7447-40-7 (potassium chloride)

L638 ANSWER 83 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
STN

ACCESSION NUMBER: 2003:143405 BIOSIS
 DOCUMENT NUMBER: PREV200300143405
 TITLE: Hepatocyte (HGF) and keratinocyte growth factor (KGF)
 differentially regulate MAP-kinases (Erk1/2, P38 and JNK):
 evidence of a cross-talk between Erk1/2 and P38 in
 corneal epithelial cells:.
 AUTHOR(S): Sharma, G. D. [Reprint Author]; He, J. C. [Reprint Author];
 Bazan, H. E. P. [Reprint Author]
 CORPORATE SOURCE: Ophthalmology and Neuroscience, LSU Health Sciences Center,
 New Orleans, LA, USA
 SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
 (2002) Vol. 2002, pp. Abstract No. 1634. cd-rom.
 Meeting Info.: Annual Meeting of the Association For
 Research in Vision and Ophthalmology. Fort Lauderdale,
 Florida, USA. May 05-10, 2002.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 19 Mar 2003
 Last Updated on STN: 19 Mar 2003

ED Entered STN: 19 Mar 2003
 Last Updated on STN: 19 Mar 2003

AB Purpose: HGF and KGF receptor stimulation induces activation of two main pathways in **corneal** epithelium: The PI3K-p706SK and the MAP-kinase Erk1/2 pathway (Exp Eye Res, 2001, 73:201 and IOVS, 1998, 39:1329). We investigated the involvement of another set of MAP-kinases, the P38 and JNK, in response to growth factors. We also examined the possible cross-talk between Erk1/2 and P38 and the action of P38 in **corneal** wound healing. Methods: Primary cultures of rabbit and immortalized human **corneal** epithelial cells were stimulated with HGF and KGF (20 ng/ml) for different times. In some experiments, 50 μ M PD98059 was added 1 hour before stimulation. Activation of p-Erk1/2, p-P38 and p-JNK1/2 was evaluated by Western blotting using phospho-specific antibodies. In organ-culture experiments, rabbit **corneas** were wounded with 7-mm epithelial debridement. **Corneas** were treated with the P38 inhibitor SB203580 (20 μ M) and with HGF (20 ng/ml) for 24 hours. Areas uncovered by epithelium were measured by image analysis. Immunofluorescence was performed in human cells with specific antibodies. Sheep anti-mouse Ig-FITC was used as secondary antibody, and nuclei were stained with DAPI. Results: HGF and KGF stimulated the phosphorylation of P38, while there was no change in total P38. Activation occurs at 15 minutes and was sustained up to 60 minutes. No activation of JNK1/2 was found. The activation of P38 was weaker than that observed with Erk1/2. Immunofluorescence of HGF- and KGF-stimulated human cells showed p-P38 staining in the perinuclear region and p-Erk1/2 staining in the nuclei. Preincubation of cells with PD98059 and their subsequent stimulation with HGF resulted in a inhibition of p-Erk1/2 and a significant stimulation of p-P38. Immunostaining showed a higher number of cells with p-P38 in the perinuclear region compared to HGF stimulation alone. Similar treatment did not stimulate JNK1/2. In rabbit **corneal** organ culture inhibition of P38 activation with SB203580 significantly delayed ($p < 0.05$) the wound closure stimulated by HGF. Conclusions: Our results demonstrate that HGF and KGF stimulate the P38 MAP-kinases in **corneal** epithelial cells. The translocation of p-P38 to the perinuclear area, stimulated by the growth factors, indicated that this kinase may phosphorylate nuclear targets. The existence of differential activation and cross-talk between Erk1/2 and P38 may be significant in modulation of **corneal** wound healing (Supported by NIH-NEI EY06635).

CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004

IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
corneal epithelial cell: sensory system

IT Chemicals & Biochemicals
 Erk1 [extracellular signal-regulated kinase 1]; Erk2 [extracellular signal-regulated kinase 2]; JNK1; JNK2; MAP kinase [EC 2.7.1.37]; P38; SB203580: enzyme inhibitor-drug; hepatocyte growth factor [HGF]; keratinocyte growth factor [KGF]; p38 MAP kinase [EC 2.7.1.37]; phospho-specific antibodies

IT Methods & Equipment
 Western blotting: genetic techniques, laboratory techniques;
 immunofluorescence: immunologic techniques, laboratory techniques

RN 137632-07-6 (Erk1)
 137632-07-6 (extracellular signal-regulated kinase 1)
 137632-08-7 (Erk2)
 137632-08-7 (extracellular signal-regulated kinase 2)
 142243-02-5 (MAP kinase)
 9026-43-1 (MAP kinase)
 142243-02-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)
 152121-47-6 (SB203580)
 148348-15-6 (keratinocyte growth factor)
 148348-15-6 (KGF)
 165245-96-5 (p38 MAP kinase)
 9026-43-1 (p38 MAP kinase)
 165245-96-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)

L638 ANSWER 84 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
 STN

ACCESSION NUMBER: 2001:310651 BIOSIS
 DOCUMENT NUMBER: PREV200100310651
 TITLE: Multiple signaling pathways and sustained IL-1alpha
 expression are required in fibrotic **corneal**
 stroma.
 AUTHOR(S): Jung, J. C. [Reprint author]; Stramer, B. M. [Reprint
 author]; Fini, M. E. [Reprint author]
 CORPORATE SOURCE: Vision Research Laboratories, New England Eye Center, Tufts
 University School of Medicine, Boston, MA, USA
 SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S902. print.
 Meeting Info.: Annual Meeting of the Association for
 Research in Vision and Ophthalmology. Fort Lauderdale,
 Florida, USA. April 29-May 04, 2001.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 27 Jun 2001
 Last Updated on STN: 19 Feb 2002
 ED Entered STN: 27 Jun 2001
 Last Updated on STN: 19 Feb 2002
 CC Enzymes - General and comparative studies: coenzymes 10802
 General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006
 IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs
 (Sensory Reception)
 IT Parts, Structures, & Systems of Organisms
 IL-1-alpha, expression, interleukin-1-alpha; **cornea**: sensory
 system; **corneal** stroma: sensory system; **corneal**
 stromal cell: sensory system; fibroblast
 IT Diseases
 fibrotic **corneal** stroma: **eye** disease
 IT Chemicals & Biochemicals
 ERK 1/2 [extracellular signal-regulated kinase 1/2]: activation; ERK
 inhibitor [extracellular signal-regulated kinase inhibitor]; IL-1
 receptor antagonist [interleukin-1 receptor antagonist]; JNK [c
 -Jun N-terminal kinase]:
 activation; MEK inhibitor [mitogen activated protein kinase kinase]

inhibitor]; NF-kappaB [nuclear factor-kappa-B]: activation;
 collagenase: regulation, synthesis; p38 MAP kinase [p38
 mitogen-activated protein kinase]: activation; p38 MAP kinase inhibitor
 [p38 mitogen-activated protein kinase inhibitor]; trephine

IT Miscellaneous Descriptors
 multiple signaling pathway; Meeting Abstract

ORGN Classifier
 Leporidae 86040
 Super Taxa
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rabbit: animal model
 Taxa Notes
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman
 Mammals, Vertebrates

RN 9001-12-1 (collagenase)
 165245-96-5 (p38 MAP kinase)
 165245-96-5 (p38 mitogen-activated protein kinase)
 155215-87-5 (C-JUN N-TERMINAL
 KINASE)

L638 ANSWER 85 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
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ACCESSION NUMBER: 2001:344414 BIOSIS
 DOCUMENT NUMBER: PREV200100344414
 TITLE: The bacterial toxin lipoteichoic acid selectively activates
 the MAP kinase pathway in the **cornea**.
 AUTHOR(S): Kiel, R. [Reprint author]; You, L. [Reprint author];
 Schmitz, L.; Kruse, F. E. [Reprint author]
 CORPORATE SOURCE: Dep. of Ophthalmology, University of Heidelberg,
 Heidelberg, Germany
 SOURCE: IOVS, (March 15, 2001) Vol. 42, No. 4, pp. S586. print.
 Meeting Info.: Annual Meeting of the Association for
 Research in Vision and Ophthalmology. Fort Lauderdale,
 Florida, USA. April 29-May 04, 2001. Association for
 Research in Vision and Ophthalmology.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 25 Jul 2001
 Last Updated on STN: 19 Feb 2002

ED Entered STN: 25 Jul 2001
 Last Updated on STN: 19 Feb 2002

CC Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
 General biology - Symposia, transactions and proceedings 00520
 Genetics - Human 03508
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004
 Toxicology - General and methods 22501
 Physiology and biochemistry of bacteria 31000
 Genetics of bacteria and viruses 31500

IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs
 (Sensory Reception); Toxicology

IT Parts, Structures, & Systems of Organisms
cornea: sensory system; **corneal keratocyte**
 : sensory system

IT Chemicals & Biochemicals

DNA; ERK 1/2 [extracellular signal-regulated kinase 1/2]: activation;
 Elk 1: activation; FAK [focal adhesion kinase]: activation; JNK [
c-Jun N-terminal kinase
]: activation; MAP kinase [mitogen-activated protein kinase]; MEK 1/2
 [mitogen activated protein kinase kinase 1/2]: activation; NF-KB
 [nuclear factor-kappa-B]: activation; TNF-alpha [tumor necrosis
 factor-alpha]; c-Raf: activation; **corneal** gene:
 transcription; lipoteichoic acid: bacterial toxin; p38: activation;
 serum response element

IT Miscellaneous Descriptors
 signal transduction pathway: activation; Meeting Abstract

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
 Micrococcaceae 07702
 Super Taxa
 Gram-Positive Cocci; Eubacteria; Bacteria; Microorganisms
 Organism Name
 Staphylococcus aureus: toxin source
 Taxa Notes
 Bacteria, Eubacteria, Microorganisms

RN 142243-02-5 (MAP kinase)
 142243-02-5 (mitogen-activated protein kinase)
 144114-16-9 (FOCAL ADHESION KINASE)
 155215-87-5 (C-JUN N-TERMINAL
KINASE)

GEN luciferase gene: reporter

L638 ANSWER 86 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
 STN

ACCESSION NUMBER: 2000:274473 BIOSIS

DOCUMENT NUMBER: PREV200000274473

TITLE: MAPK involvement in recovery of paracellular resistance
 during exposure to a hypertonic challenge in cultured
 rabbit and human **corneal** epithelial layers.

AUTHOR(S): Wang, Z. [Reprint author]; Bildin, V. N. [Reprint author];
 Reinach, P. S. [Reprint author]

CORPORATE SOURCE: Biological Sciences, College of Optometry, SUNY, New York,
 NY, USA

SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S903. print.
 Meeting Info.: Annual Meeting of the Association in Vision
 and Ophthalmology. Fort Lauderdale, Florida, USA. April
 30-May 05, 2000. Association for Research in Vision and
 Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 30 Jun 2000

Last Updated on STN: 5 Jan 2002

ED Entered STN: 30 Jun 2000

Last Updated on STN: 5 Jan 2002

CC Sense organs - General and methods 20001

Biochemistry studies - General 10060

Biophysics - General 10502

General biology - Symposia, transactions and proceedings 00520
 IT Major Concepts
 Sense Organs (Sensory Reception)
 IT Parts, Structures, & Systems of Organisms
 corneal epithelium: sensory system, layers, paracellular
 resistance
 IT Chemicals & Biochemicals
 SAPK/JNK [stress-activated protein kinase/c-Jun
 N-terminal kinase]; mitogen-activated
 protein kinase; p38; p44/42
 IT Miscellaneous Descriptors
 hypertonic stress; Meeting Abstract
 ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
 ORGN Classifier
 Leporidae 86040
 Super Taxa
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rabbit
 Taxa Notes
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman
 Mammals, Vertebrates
 RN 142243-02-5 (mitogen-activated protein kinase)

L638 ANSWER 87 OF 94 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on
 STN
 ACCESSION NUMBER: 1999:235590 BIOSIS
 DOCUMENT NUMBER: PREV199900235590
 TITLE: Involvement of K⁺ channel activity in ultraviolet-induced
 apoptosis through the JNK pathway in rabbit corneal
 epithelial cells.
 AUTHOR(S): Wang, L. [Reprint author]; Shell, B. [Reprint author]; Lu,
 L. [Reprint author]
 CORPORATE SOURCE: Department of Physiology and Biophysics, Wright State
 University School of Medicine, Dayton, OH, USA
 SOURCE: IOVS, (March 15, 1999) Vol. 40, No. 4, pp. S100. print.
 Meeting Info.: Annual Meeting of the Association for
 Research in Vision and Ophthalmology. Fort Lauderdale,
 Florida, USA. May 9-14, 1999. Association for Research in
 Vision and Ophthalmology.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 Conference; (Meeting Poster)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 17 Jun 1999
 Last Updated on STN: 17 Jun 1999
 ED Entered STN: 17 Jun 1999
 Last Updated on STN: 17 Jun 1999
 CC Sense organs - General and methods 20001
 Cytology - Animal 02506
 Radiation biology - General 06502
 Biochemistry studies - General 10060
 Pathology - Necrosis 12510

Biophysics - General 10502
 General biology - Symposia, transactions and proceedings 00520
 IT Major Concepts
 Biochemistry and Molecular Biophysics; Sense Organs (Sensory Reception)
 IT Parts, Structures, & Systems of Organisms
 corneal epithelial cells: sensory system, mitogen-activated
 proliferation; corneal epithelium: sensory system
 IT Diseases
 corneal epithelial damage: eye disease
 IT Chemicals & Biochemicals
 potassium ion channel: 4-aminopyridine-sensitive, voltage-gated; JNK [c-Jun N-terminal kinase]: activation, pathway
 IT Miscellaneous Descriptors
 apoptosis: ultraviolet-induced; Meeting Abstract; Meeting Poster; UV irradiation
 ORGN Classifier
 Leporidae 86040
 Super Taxa
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rabbit
 Taxa Notes
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Vertebrates
 RN 504-24-5 (4-AMINOPYRIDINE)
 9031-44-1 (KINASE)
 24203-36-9 (POTASSIUM ION)

L638 ANSWER 88 OF 94 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-30083 DRUGU P B V

TITLE: Inhibition of p38MAP kinase potentiates the JNK/SAPK pathway and AP-1 activity in monocytic but not macrophage or granulocytic differentiation of HL60 cells.

AUTHOR: Wang X; Studzinski G P

CORPORATE SOURCE: Univ.New-Jersey-Med.Dent.

LOCATION: Newark, N.J., USA

SOURCE: J.Cell.Biochem. (82, No. 1, 68-77, 2001) 6 Fig. 2 Tab. 39 Ref.

CODEN: JCEBD5 ISSN: 0730-2312

AVAIL. OF DOC.: Department of Pathology and Laboratory Medicine, UMD-New Jersey Medical School, 185 South Orange Avenue, C543, Newark, New Jersey 07103, U.S.A. (G.P.S). (e-mail: studzins@umdnj.edu).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB The effects of 1,25-dihydroxyvitamin D3 (D3), retinoic acid (RA, Sigma-Chemical), DMSO (Sigma-Chemical) and tetradecanoylphorbol acetate (TPA, Sigma-Chemical) and p38MAPK inhibitors SB-203580 (SB203) and SB-202190 (SB202, Calbiochem-Novobiochem) on HL60-G cells were investigated in an in-vitro study. D3, RA, DMSO and TPA-induced differentiation was potentiated with SB203. In conclusion, these studies show there are profound differences between mechanisms of D3 and TPA-induced differentiation and that while the monocytic and macrophage phenotypes are enhanced by p38MAPK inhibition, only the pure monocytic differentiation induced by D3 is associated with upregulation of the JNK/c-jun pathway.

CODEN: JBCHA3 ISSN: 0021-9258
AVAIL. OF DOC.: Metabolic Disorders-Diabetes, Merck Research Laboratories,
RY80N-C31, PO Box 2000, Rahway, NJ 07065, U.S.A. (B.B.Z.).
(e-mail: bei_zhang@merck.com).

LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

AB The effects of salicylic acid (SA) on PMA- and TNF-alpha-induced insulin (INS) (all Sigma-Chemical) resistance in human embryonic kidney 293 cells stably expressing INS receptor substrate 1 (IRS1) (HEK293.IRS1 cells) were investigated in-vitro. PMA and TNF-alpha inhibited INS-induced Akt phosphorylation and promoted IRS1 phosphorylation on Ser-307. Pretreatment with SA reversed the effects of PMA and TNF-alpha on Akt and Ser-307. PMA, but not TNF-alpha, activated protein kinase C (PKC) isoforms and IKKbeta. PMA and TNF-alpha activated c-Jun N-terminal kinase (JNK). SP-600125 prevented PMA and TNF-alpha-induced IRS1 Ser-307 phosphorylation. SA inhibited JNK activation induced by PMA and TNF-alpha. These findings suggest that SA can reverse the inhibitory effects of TNF-alpha on INS signaling via an IKKbeta-independent mechanism, potentially involving the inhibition of JNK activation. e

General →
JNK-I₁₅ (Not Specific)
A

=> d que 1125

```

L102(      3)SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L103(      1)SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L104      SEL  PLU=ON  L102 1- CHEM :      11 TERMS
L105(     432)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L104
L106(     186)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L102
L107      SEL  PLU=ON  L103 1- CHEM :      13 TERMS
L108(    4144)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L107
L109(     931)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L103
L110(   35883)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE"+PFT,NT/CT
L111(   21166)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE OR DISORDER"+PFT
,NT/CT
L112(   17731)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYES, DISEASES OR DISORDERS"+
PFT,NT/CT
L113(    610)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "EYE, DISEASE (L) DRY"+PFT,NT/
CT
L114(      3)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L105 OR L106) AND (L110 OR
L111 OR L112 OR L113)
L115(     27)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L108 OR L109) AND (L110 OR
L111 OR L112 OR L113)
L116      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L117(      1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L105 OR L106) (L) L116
L118(     24)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L108 OR L109) (L) L116
L119(     47)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L114 OR L115 OR L117 OR L118
L120(     65)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L105 OR L106 OR L108 OR
L109) AND L116
L121(     68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L119 OR L120)
L122(      5)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L121 AND (L105 OR L106)
L123(     63)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L121 NOT L122
L124(     31)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L123 AND (AY<2003 OR PY<2003
OR PRY<2003)
L125      32 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L123 NOT L124

```

=> d his 1155

(FILE 'USPATFULL, USPAT2' ENTERED AT 07:40:05 ON 29 SEP 2005)

L155 5 SEA L153 NOT L154

=> d que 1155

```

L144      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L145(     21)SEA L144
L146(      8)SEA L145 AND L144/TI,IT,BI,ST,CC
L147(      9)SEA A61P027-02/IPC
L148(      0)SEA L145 AND L147
L149(      8)SEA L146 OR L148
L150(      8)SEA L149 AND (AY<2003 OR PY<2003 OR PRY<2003)
L151(     64)SEA L144
L152(     30)SEA L151 AND L144/TI,IT,BI,ST,CC
L153(     29)SEA L152 NOT L150
L154(     24)SEA L153 AND (AY<2003 OR PY<2003 OR PRY<2003)
L155      5 SEA L153 NOT L154

```


=> d que 1217

L202(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR
 RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
 L203(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
 L204(8)SEA FILE=WPIX ABB=ON PLU=ON L202 OR L203
 L205(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L206(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03
 OR B12-J08 OR C12-J08 OR E12-J08)/MC
 L207(1)SEA FILE=WPIX ABB=ON PLU=ON L204 AND (L205 OR L206)
 L208(3)SEA FILE=WPIX ABB=ON PLU=ON L204 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L209(8)SEA FILE=WPIX ABB=ON PLU=ON L204 OR L207 OR L208
 L210(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
 L211(115)SEA FILE=WPIX ABB=ON PLU=ON L210 AND (L205 OR L206)
 L212(105)SEA FILE=WPIX ABB=ON PLU=ON L211 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L213(28)SEA FILE=WPIX ABB=ON PLU=ON L212 AND ((DRY?(3A)EYE?) OR
 ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR
 ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN?
 OR ?XEROPH?)/BIX
 L214(35)SEA FILE=WPIX ABB=ON PLU=ON L209 OR L213
 L215(28)SEA FILE=WPIX ABB=ON PLU=ON L214 AND (AY<2003 OR PY<2003 OR
 PRY<2003)
 L216(24)SEA FILE=WPIX ABB=ON PLU=ON L215 AND L213
 L217 11 SEA FILE=WPIX ABB=ON PLU=ON L214 NOT L216

=> d que 1245

L232(3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L233(1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L234 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L235 SEL PLU=ON L232 1- CHEM : 11 TERMS
 L236(218)SEA FILE=MEDLINE ABB=ON PLU=ON L235
 L237(9127)SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
 L238(1)SEA FILE=MEDLINE ABB=ON PLU=ON L236 AND L234
 L239 SEL PLU=ON L233 1- CHEM : 13 TERMS
 L240(3278)SEA FILE=MEDLINE ABB=ON PLU=ON L239
 L241(2)SEA FILE=MEDLINE ABB=ON PLU=ON L240 AND L237
 L242(32)SEA FILE=MEDLINE ABB=ON PLU=ON L240 AND L234
 L243(32)SEA FILE=MEDLINE ABB=ON PLU=ON (L241 OR L242)
 L244(11)SEA FILE=MEDLINE ABB=ON PLU=ON L243 AND PY<2003
 L245 20 SEA FILE=MEDLINE ABB=ON PLU=ON L243 NOT (L244 OR L238)

=> d que 1292

L274(3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L275(1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN

L276 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L277 SEL PLU=ON L274 1- CHEM : 11 TERMS

L278 (547) SEA FILE=EMBASE ABB=ON PLU=ON L277

L279 (2325) SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT

L280 (0) SEA FILE=EMBASE ABB=ON PLU=ON L278 AND L279

L281 (1) SEA FILE=EMBASE ABB=ON PLU=ON L278 AND L276

L282 (1) SEA FILE=EMBASE ABB=ON PLU=ON (L280 OR L281)

L283 (0) SEA FILE=EMBASE ABB=ON PLU=ON L282 AND (PY<2003 OR MY<2003)

L284 (1) SEA FILE=EMBASE ABB=ON PLU=ON L282 NOT L283

L285 SEL PLU=ON L275 1- CHEM : 13 TERMS

L286 (2867) SEA FILE=EMBASE ABB=ON PLU=ON L285

L287 (2) SEA FILE=EMBASE ABB=ON PLU=ON L286 AND L279

L288 (24) SEA FILE=EMBASE ABB=ON PLU=ON L286 AND L276

L289 (24) SEA FILE=EMBASE ABB=ON PLU=ON (L287 OR L288)

L290 (24) SEA FILE=EMBASE ABB=ON PLU=ON L289 NOT L284

L291 (8) SEA FILE=EMBASE ABB=ON PLU=ON L290 AND (PY<2003 OR MY<2003)

L292 16 SEA FILE=EMBASE ABB=ON PLU=ON L290 NOT L291

=> d his 1636

(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
 VETU, VETB, SCISEARCH' ENTERED AT 07:43:51 ON 29 SEP 2005)

L636 27 SEA L582 NOT L625

=> d que 1636

L553 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L554 SEL PLU=ON L553 1- CHEM : 11 TERMS

L555 (813) SEA L554

L556 (6) SEA L555 AND L553

L557 (6) DUP REM L556 (0 DUPLICATES REMOVED)

L558 SEL PLU=ON L553 1- CHEM : 13 TERMS

L559 (13886) SEA L558

L560 (139) SEA L559 AND L553

L561 (88) DUP REM L560 (51 DUPLICATES REMOVED)

L562 (55) SEA FILE=BIOSIS L561

L563 (25) SEA FILE=BIOSIS L562 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L564 (6) SEA FILE=TOXCENTER L561

L565 (2) SEA FILE=TOXCENTER L564 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L566 (8) SEA FILE=PASCAL L561

L567 (2) SEA FILE=PASCAL L566 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L568 (0) SEA FILE=JICST-EPLUS L561

L569 (0) SEA FILE=JICST-EPLUS L568 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)

L570 (0) SEA FILE=LIFESCI L561

L571 (0) SEA FILE=LIFESCI L570 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?

OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L572(1)SEA FILE=CANCERLIT L561
 L573(1)SEA FILE=CANCERLIT L572 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L574(11)SEA FILE=DRUGU L561
 L575(11)SEA FILE=DRUGU L574 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L576(0)SEA FILE=VETU L561
 L577(0)SEA FILE=VETU L576 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L578(0)SEA FILE=VETB L561
 L579(0)SEA FILE=VETB L578 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L580(7)SEA FILE=SCISEARCH L561
 L581(3)SEA FILE=SCISEARCH L580 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
 OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L582(44)SEA L561 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR
 LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
 ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
 L583(3)SEA FILE=BIOSIS L557
 L584(28)SEA FILE=BIOSIS L583 OR L563
 L585(0)SEA FILE=TOXCENTER L557
 L586(2)SEA FILE=TOXCENTER L585 OR L565
 L587(0)SEA FILE=PASCAL L557
 L588(2)SEA FILE=PASCAL L587 OR L567
 L589(0)SEA FILE=JICST-EPLUS L557
 L590(0)SEA FILE=JICST-EPLUS L589 OR L569
 L591(0)SEA FILE=LIFESCI L557
 L592(0)SEA FILE=LIFESCI L591 OR L571
 L593(0)SEA FILE=CANCERLIT L557
 L594(1)SEA FILE=CANCERLIT L593 OR L573
 L595(3)SEA FILE=DRUGU L557
 L596(12)SEA FILE=DRUGU L595 OR L575
 L597(0)SEA FILE=VETU L557
 L598(0)SEA FILE=VETU L597 OR L577
 L599(0)SEA FILE=VETB L557
 L600(0)SEA FILE=VETB L599 OR L579
 L601(0)SEA FILE=SCISEARCH L557
 L602(3)SEA FILE=SCISEARCH L601 OR L581
 L603(48)SEA L557 OR L582
 L604(9)SEA FILE=BIOSIS L584 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L605(0)SEA FILE=TOXCENTER L586 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L606(0)SEA FILE=PASCAL L588 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L607(0)SEA FILE=JICST-EPLUS L590 AND (AY<2003 OR PY<2003 OR PRY<2003
 OR MY<2003)
 L608(0)SEA FILE=LIFESCI L592 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L609(1)SEA FILE=CANCERLIT L594 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L610(7)SEA FILE=DRUGU L596 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 MY<2003)
 L611(0)SEA FILE=VETU L598 AND (AY<2003 OR PY<2003 OR PRY<2003 OR

MY<2003)
L612(0)SEA FILE=VETB L600 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
MY<2003)
L613(1)SEA FILE=SCISEARCH L602 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
MY<2003)
L614(18)SEA L603 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L615(9)SEA FILE=BIOSIS L604 AND L563
L616(0)SEA FILE=TOXCENTER L605 AND L565
L617(0)SEA FILE=PASCAL L606 AND L567
L618(0)SEA FILE=JICST-EPLUS L607 AND L569
L619(0)SEA FILE=LIFESCI L608 AND L571
L620(1)SEA FILE=CANCERLIT L609 AND L573
L621(6)SEA FILE=DRUGU L610 AND L575
L622(0)SEA FILE=VETU L611 AND L577
L623(0)SEA FILE=VETB L612 AND L579
L624(1)SEA FILE=SCISEARCH L613 AND L581
L625(17)SEA L614 AND L582
L626 16 SEA FILE=BIOSIS L563 NOT L615
L627 2 SEA FILE=TOXCENTER L565 NOT L616
L628 2 SEA FILE=PASCAL L567 NOT L617
L629(0)SEA FILE=JICST-EPLUS L569 NOT L618
L630(0)SEA FILE=LIFESCI L571 NOT L619
L631(0)SEA FILE=CANCERLIT L573 NOT L620
L632 5 SEA FILE=DRUGU L575 NOT L621
L633(0)SEA FILE=VETU L577 NOT L622
L634(0)SEA FILE=VETB L579 NOT L623
L635 2 SEA FILE=SCISEARCH L581 NOT L624
L636 27 SEA L582 NOT L625

=> dup rem l125 l155 l217 l245 l292 l636
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FILE 'SCISEARCH' ENTERED AT 08:01:10 ON 29 SEP 2005

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PROCESSING COMPLETED FOR L125

PROCESSING COMPLETED FOR L155

PROCESSING COMPLETED FOR L217

PROCESSING COMPLETED FOR L245

PROCESSING COMPLETED FOR L292

PROCESSING COMPLETED FOR L636

L640 79 DUP REM L125 L155 L217 L245 L292 L636 (32 DUPLICATES REMOVED)

ANSWERS '1-32' FROM FILE HCAPLUS

ANSWERS '33-37' FROM FILE USPATFULL

ANSWERS '38-48' FROM FILE WPIX

ANSWERS '49-60' FROM FILE MEDLINE

ANSWERS '61-63' FROM FILE EMBASE

ANSWERS '64-71' FROM FILE BIOSIS

ANSWER '72' FROM FILE TOXCENTER

ANSWERS '73-77' FROM FILE DRUGU

ANSWERS '78-79' FROM FILE SCISEARCH

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 08:01:40 ON 29 SEP 2005

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FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Sep 23, 2005 (20050923/UP).

=> d ibib ed ab hitind hitstr 1-32

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L640 ANSWER 1 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 1

ACCESSION NUMBER: 2005:1029993 HCAPLUS
TITLE: Non-cell-autonomous induction of tissue overgrowth by JNK/Ras cooperation in a Drosophila tumor model
AUTHOR(S): Uhlirova, Mirka; Jasper, Heinrich; Bohmann, Dirk
CORPORATE SOURCE: Department of Biomedical Genetics, University of Rochester Medical Center, Rochester, NY, 14642, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2005), 102(37), 13123-13128
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 26 Sep 2005

AB The role of **c-Jun N-terminal**

kinase (JNK) signaling in cancer is enigmatic, and both tumor-promoting and tumor-suppressing functions have been ascribed to JNK pathway components. We have used the Drosophila **eye** to investigate the function of the JNK pathway in three different tumor models of increasing malignancy. Benign lesions caused by loss of the neoplastic tumor suppressor gene scribble can efficiently be eliminated by JNK-induced apoptosis. In such a scenario, the **eye** reverts to a wild-type phenotype, indicating that the JNK pathway prevents tumor formation. The situation changes in the case of aggressive tissue overgrowth, which can be induced by oncogenic activation of the Ras/Raf pathway in the **eye**, or in malignant invasive tumors resulting when Raf activation is combined with loss of scribble. The growth of these more aggressive tumor types is significantly, yet incompletely, suppressed by JNK-mediated apoptosis. Remarkably, oncogenic Raf and JNK cooperate in these tumors, to induce massive hyperplasia in adjacent wild-type tissue. Thus, depending on the genetic context, JNK signaling can eradicate tumors by removing premalignant cells, or promote aberrant overgrowth in tissues surrounding primary lesions.

CC 12 (Nonmammalian Biochemistry)

L640 ANSWER 2 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2005:455567 HCAPLUS
DOCUMENT NUMBER: 143:186615
TITLE: Therapeutic effect of topical administration of SN50, an inhibitor of nuclear factor- κ B, in treatment of **corneal** alkali burns in mice
AUTHOR(S): Saika, Shizuya; Miyamoto, Takeshi; Yamanaka, Osamu; Kato, Tadashi; Ohnishi, Yoshitaka; Flanders, Kathleen C.; Ikeda, Kazuo; Nakajima, Yuji; Kao, Winston W.-Y.; Sato, Misako; Muragaki, Yasuteru; Ooshima, Akira
CORPORATE SOURCE: Department of Ophthalmology, Wakayama Medical University, Wakayama, Japan
SOURCE: American Journal of Pathology (2005), 166(5), 1393-1403
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 May 2005

- AB We evaluated the therapeutic efficacy of topical administration of SN50, an inhibitor of nuclear factor- κ B, in a **corneal alkali burn** model in mice. An alkali burn was produced with 1 N NaOH in the **cornea** of C57BL/6 mice under general anesthesia. SN50 (10 μ g/ μ l) or vehicle was topically administered daily for up to 12 days. The **eyes** were processed for histol. or immunohistochem. examination after bromode-oxyuridine labeling or for semiquantification of cytokine mRNA. Topical SN50 suppressed nuclear factor- κ B activation in local cells and reduced the incidence of epithelial defects/ulceration in healing **corneas**. Myofibroblast generation, macrophage invasion, activity of matrix metalloproteinases, basement membrane destruction, and expression of cytokines were all decreased in treated **corneas** compared with controls. To elucidate the role of tumor necrosis factor (TNF)- α in epithelial cell proliferation, we performed organ culture of mouse **eyes** with TNF- α , SN50, or an inhibitor of **c-Jun N-terminal kinase** (JNK) and examined cell proliferation in healing **corneal** epithelium in TNF- α -/- mice treated with SN50. An acceleration of epithelial cell proliferation by SN50 treatment was found to depend on TNF- α /JNK signaling. In conclusion, topical application of SN50 is effective in treating **corneal alkali burns** in mice.
- CC 1-12 (Pharmacology)
- ST SN50 nuclear factor kappa B **cornea** burn
- IT Cyclins
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (D1; SN50 topical administration increased cyclin D1 expression in nucleus of healing epithelial cells in mouse model of **corneal alkali burn**)
- IT Transcription factors
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (NF- κ B (nuclear factor of κ light chain gene enhancer in B-cells); NF- κ B inhibitor SN50 topical administration was effective in treating **corneal alkali burn** by blocking TNF- α /JNK pathway and by reducing macrophage invasion, myofibroblast generation, cytokine expression, BM destruction in mouse model)
- IT Drug targets
Eye
 (NF- κ B inhibitor SN50 topical administration was effective in treating **corneal alkali burn** by blocking TNF- α /JNK pathway and by reducing macrophage invasion, myofibroblast generation, cytokine expression, BM destruction in mouse model)
- IT Monocyte chemoattractant protein-1
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (SN50 topical administration decreased MCP-1 mRNA expression in healing epithelium, stromal **keratocytes**, stromal matrix in mouse model of **corneal alkali burn**)
- IT Chemokines
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (SN50 topical administration decreased chemokine MCP-1 mRNA expression in healing epithelium, stromal **keratocytes**, stromal matrix in mouse model of **corneal alkali burn**)
- IT Macrophage
 Monocyte
 (SN50 topical administration decreased number of monocytes/macrophages in **cornea** in mouse model of **corneal alkali burn**)
- IT Apoptosis
 (SN50 topical administration did not affect apoptosis in epithelial cells in **cornea** in mouse **corneal alkali burn** model)

- IT Signal transduction, biological
(SN50 topical administration effectively blocked phosphorylation and nuclear translocation of p65 subunit of NF- κ B in healing epithelium, stromal cells and suppressed NF- κ B signaling in mouse model of **corneal alkali burn**)
- IT Laminins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SN50 topical administration inhibited expression of laminin in epithelial basement membrane and stroma in mouse model of **corneal alkali burn**)
- IT Basement membrane
(SN50 topical administration preserved basement membrane components type IV collagen but inhibited expression of laminin in stroma in mouse model of **corneal alkali burn**)
- IT Transforming growth factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SN50 topical administration suppressed expression of extracellular secreted transforming growth factor- β 1 and - β 2 in **cornea** in mouse model of **corneal alkali burn**)
- IT Wound healing
(SN50 topical administration was efficacious in treating **corneal alkali burn** by blocking TNF- α /JNK pathway and by decreasing macrophage invasion, myofibroblast generation, cytokine expression, MMP activity, BM destruction in mouse model)
- IT Cell proliferation
(SN50-induced cell proliferation was suppressed in TNF- α null mouse and by JNK inhibitor in mouse **eye** showing blocking TNF- α /JNK pathway accelerated proliferation in healing epithelium in mouse model of **corneal alkali burn**)
- IT **Eye**
(**cornea**; SN50 topical administration was efficacious in treating **corneal alkali burn** by blocking TNF- α /JNK pathway and by decreasing macrophage invasion, myofibroblast generation, cytokine expression, MMP activity, BM destruction in mouse model)
- IT **Burn**
(**eye**; SN50 topical administration was efficacious in treating **corneal alkali burn** by blocking TNF- α /JNK pathway and by decreasing macrophage invasion, myofibroblast generation, cytokine expression, MMP activity, BM destruction in mouse model)
- IT Collagens, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(type IV; SN50 topical administration preserved epithelial basement membrane type IV collagen in mouse model of **corneal alkali burn**)
- IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(α -smooth muscle; SN50 topical administration decreased α -smooth muscle actin-expressing myofibroblast in mouse model of **corneal alkali burn**)
- IT 146480-36-6, Matrix metalloproteinase-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SN50 topical administration suppressed up-regulation of matrix metalloproteinase-9 mRNA expression in mouse model of **corneal alkali burn**)
- IT 140208-24-8, Tissue inhibitor of metalloproteinase-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(SN50 topical administration suppressed up-regulation of tissue inhibitor of metalloproteinase-1 mRNA expression in mouse model of **corneal alkali burn**)

IT 372485-58-0, SN 50
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (SN50 topical administration was efficacious in treating corneal alkali burn by blocking TNF- α /JNK pathway and by decreasing macrophage invasion, myofibroblast generation, cytokine expression, MMP activity, BM destruction in mouse model)

IT 155215-87-5, c-Jun N-terminal kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study) (c-Jun N-terminal kinase inhibitor inhibited topically administered SN50-induced cell proliferation acceleration in organ culture of mouse eye indicating tumor necrosis factor- α /JNK pathway accelerated proliferation in mouse eye)

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640/ANSWER 3 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 3

ACCESSION NUMBER: 2005:374625 HCAPLUS

DOCUMENT NUMBER: 143:41119

TITLE: JNK and ROK α function in the noncanonical Wnt/RhoA signaling pathway to regulate Xenopus convergent extension movements

AUTHOR(S): Kim, Gun-Hwa; Han, Jin-Kwan

CORPORATE SOURCE: Division of Molecular and Life Sciences, Pohang University of Science and Technology, Hyoja Dong, Pohang, Kyungbuk, S. Korea

SOURCE: Developmental Dynamics (2005), 232(4), 958-968

CODEN: DEDYEI; ISSN: 1058-8388

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 02 May 2005

AB The Wnt/planar cell polarity (PCP) pathway plays a critical role in wing, eye, and sensory bristle development of Drosophila and in convergent extension (CE) movements during vertebrate gastrulation. In Drosophila, Jun N-terminal kinase (JNK) and Rho-associated kinase (ROK) participate in RhoA-mediated PCP pathway during eye and wing development. In mammalian cells, Rac1 and Cdc42 but not RhoA are required for JNK activation by Wnt/PCP signals. However, there has been no evidence that Rho GTPases regulate JNK activation in Wnt/PCP pathway during Xenopus CE movements. Here, we report that Xenopus RhoA (XRhoA), but not Xenopus Cdc42 (XCdc42), is essential for JNK activation downstream of the Wnt/PCP pathway during Xenopus CE movements, and the phenotypic effect of loss of XRhoA function was rescued by Xenopus JNK1 (XeJNK1). In addition, XRhoA rescues the inhibition of CE movements by the DEP domain deletion mutant of Xenopus Dsh (Xdsh- Δ DEP), which has dominant neg. (DN) effects on JNK activation, and the PDZ domain deletion mutant of Xdsh (Xdsh- Δ PDZ). Moreover, we demonstrate that Xenopus Rho-associated kinase α (xROK α), which is expressed mainly in mesoderm and ectoderm that undergo extensive cell rearrangements, regulates CE movements without affecting gene expression, and injection of xROK α rescued the inhibition of CE movements caused by DN XRhoA. Finally, we show that ROK α and JNK synergistically rescued embryos overexpressing DN XRhoA, which exhibit gastrulation defects, although ROK α is not required for JNK activation. Together, these data suggest that JNK and ROK α function in the noncanonical Wnt/RhoA pathway to regulate Xenopus CE movements.

CC 12-3 (Nonmammalian Biochemistry)

IT 182938-08-5, Rho A binding kinase α 289898-51-7,
Jun N-terminal kinase 1
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (JNK and ROK α function in noncanonical Wnt/RhoA signaling pathway
 to regulate *Xenopus* convergent extension movements)

IT 289898-51-7, **Jun N-terminal**
kinase 1
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (JNK and ROK α function in noncanonical Wnt/RhoA signaling pathway
 to regulate *Xenopus* convergent extension movements)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 4 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 6

ACCESSION NUMBER: 2005:194788 HCAPLUS

DOCUMENT NUMBER: 142:461407

TITLE: The mitogen-activated protein kinases p38 and ERK1/2
 are increased in lesional psoriatic skin

AUTHOR(S): Johansen, C.; Kragballe, K.; Westergaard, M.;
 Henningsen, J.; Kristiansen, K.; Iversen, L.

CORPORATE SOURCE: Department of Dermatology, Marselisborg Hospital,
 University of Aarhus, Aarhus C, DK-8000, Den.

SOURCE: British Journal of Dermatology (2005), 152(1), 37-42
 CODEN: BJDEAZ; ISSN: 0007-0963

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 06 Mar 2005

AB Alterations in specific signal transduction pathways may explain the
 hyperproliferation and abnormal differentiation of the keratinocytes as
 well as the increased expression of inflammatory cytokines seen in
 psoriasis. Major signalling pathways used by eukaryotic cells to
 transduce extracellular signals into cellular responses impinge on the
 mitogen-activated protein kinases (MAPKs). To investigate the expression
 of the MAPK p38, extracellular signal-regulated kinase (ERK) and c-Jun
 NH2-terminal kinase (JNK) in psoriatic skin. **Keratome** biopsies
 were taken from patients with plaque-type psoriasis. Western blot anal.
 was used to determine p38, ERK and JNK activity and protein levels, whereas
 kinase assays were used to examine the kinase activity of p38. We
 demonstrated increased levels of the phosphorylated forms of p38 and
 ERK1/2 in lesional psoriatic skin compared with nonlesional psoriatic
 skin. No abnormality was found in the activation and expression of
 JNK1/2. Ex vivo kinase assays confirmed the increased activation
 of p38, and furthermore demonstrated increased kinase activity of the p38
 isoforms p38 α , p38 β and p38 δ in lesional compared with
 nonlesional psoriatic skin. P38 γ was not detected in the psoriatic
 skin. Clearance of the psoriatic lesions, induced by climatotherapy at
 the Dead Sea for 4 wk, led to a normalization in the activity of both p38
 and ERK1/2. Taken together, our results demonstrate that the activity of
 the MAPKs p38 α , p38 β and p38 δ and ERK1/2 are increased in
 lesional psoriatic skin compared with nonlesional psoriatic skin, and that
 clearance of psoriasis normalizes the p38 and ERK1/2 activity. Thus, p38
 and ERK1/2 might be potential targets in the treatment of psoriasis.

CC 14-9 (Mammalian Pathological Biochemistry)

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 5 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 10

ACCESSION NUMBER: 2004:1050125 HCAPLUS

DOCUMENT NUMBER: 142:52841

TITLE: Zn²⁺-induced cell death is mediated by the induction of intracellular ROS in ARPE-19 cells

AUTHOR(S): Song, Jeongmin; Lee, Sung Chul; Kim, Sung Soo; Koh, Hyung J.; Kwon, Oh Woong; Kang, Jimmy Jaeyoung; Kim, Eung Kweon; Shin, Seung-Hun; Lee, Joon H.

CORPORATE SOURCE: Department of Ophthalmology, Institute of Vision Research, Yonsei University College of Medicine, Seoul, S. Korea

SOURCE: Current Eye Research (2004), 28(3), 195-201

CODEN: CEYRDM; ISSN: 0271-3683

PUBLISHER: Taylor & Francis The Netherlands

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 08 Dec 2004

AB Recent studies have shown that Zn²⁺ induced cell death in retinal pigment epithelial cells. Here we sought to investigate the mode of Zn²⁺-induced cell death and the role of reactive oxygen species (ROS) in human retinal pigment epithelial cell line, ARPE-19 cells. Cell viability was measured by MTT assay. Cell death of ARPE-19 cells was measured by annexin V-fluorescein isothiocyanate (FITC) binding assay, TUNEL assay. The formation of intracellular ROS was measured using 2',7'-dichlorofluorescein diacetate (DCFH-DA). The activation of mitogen-activated protein kinase (MAPK) was examined by Western blot anal. This study demonstrated that Zn²⁺ treatment induced both necrosis and apoptosis in ARPE-19 cells. Exposure of ARPE-19 cells to Zn²⁺ led to the activation of ERK1/2, JNK1/2/3, and p38 MAPKs. The activation of these MAPKs was blocked by treatment with the antioxidant, N-acetylcystein (NAC). More importantly, inhibition of ROS production by NAC completely prevented Zn²⁺-induced cell death in RPE cells. This study suggests that Zn²⁺ induces both apoptosis and necrosis in ARPE-19 cells and that its cytotoxicity may depend on the induction of intracellular ROS.

CC 13-6 (Mammalian Biochemistry)

ST zinc retina pigment epithelium apoptosis oxidative stress; ERK1 ERK2 kinase zinc eye pigment epithelium necrosis; reactive oxygen JNK1 JNK2 JNK3 kinase eye apoptosis; p38 MAP kinase retina pigment epithelium apoptosis oxidative stress

IT Eye (pigment epithelium; involvement of mitogen-activated protein kinases in Zn²⁺-induced cell death mediated by induction of intracellular ROS in human ARPE-19 cells)

IT 7440-66-6, Zinc, biological studies 137632-07-6, ERK1 kinase 137632-08-7, ERK2 kinase 165245-96-5, P38 MAP kinase 289898-51-7, JNK1 kinase 289899-93-0, JNK2 kinase 291756-39-3, JNK3 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (involvement of mitogen-activated protein kinases in Zn²⁺-induced cell death mediated by induction of intracellular ROS in human ARPE-19 cells)

IT 289898-51-7, JNK1 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (involvement of mitogen-activated protein kinases in Zn²⁺-induced cell death mediated by induction of intracellular ROS in human ARPE-19 cells)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 6 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 11

ACCESSION NUMBER: 2003:443564 HCAPLUS

DOCUMENT NUMBER: 139:160359

TITLE: p38 and ERK1/2 coordinate cellular migration and
proliferation in epithelial wound healing: evidence of
cross-talk activation between MAP kinase cascades

AUTHOR(S): Sharma, Guru-Dutt; He, Jiucheng; Bazan, Haydee E. P.

CORPORATE SOURCE: Department of Ophthalmology and Neuroscience Center of
Excellence, Louisiana State University Health Sciences
Center, New Orleans, LA, 70112, USA

SOURCE: Journal of Biological Chemistry (2003), 278(24),
21989-21997

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular
Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Jun 2003

AB One important action of growth factors is their participation in tissue
repair; however, the signaling pathways involved are poorly understood.
In a model of **corneal** wound healing, we found that two paracrine
growth factors, hepatocyte growth factor (HGF) and keratinocyte growth
factor (KGF), induced rapid and marked activation and prompt nuclear
accumulation of phospho-p38 (p-p38) and -ERK1/2 (p-ERK1/2), but not of JNK
(p-JNK1/2), in **corneal** epithelial cells. Interruption
of p38 and ERK1/2 signaling pathways by pretreatment with inhibitors
SB203580 and PD98059 and subsequent stimulation with HGF or KGF abolished
the activation and nuclear localization. Inhibition of either one of
these mitogen-activated protein kinases, p38 or ERK1/2, induced a robust
cross-activation of the other. In immunofluorescence studies of wounded
cornea, p-p38, unlike p-ERK1/2, was immediately detectable in
epithelium after injury. Inhibition of p38 by SB203580 blocked migration
of epithelial cells almost completely. In contrast, PD98059 seemed to
slightly increase the migration, through concomitant activation of p38.
Unlike ERK1/2, p38 did not significantly contribute to proliferation of
epithelial cells. Inhibition of either the ERK1/2 or p38 pathway resulted
in delayed **corneal** epithelial wound healing. Interruption of
both signaling cascades additively inhibited the wound-healing process.
These findings demonstrate that both p38 and ERK1/2 coordinate the
dynamics of wound healing: while growth factor-stimulated p38 induces
epithelial migration, ERK1/2 activation induces proliferation. The
cross-talk between these two signal cascades and the selective action of
p38 in migration appear to be important to **corneal** wound
healing, and possibly wound healing in general, and may offer novel drug
targets for tissue repair.

CC 2-10 (Mammalian Hormones)

Section cross-reference(s): 14

IT Human

(cell line; p38 and ERK1/2 coordinate cellular migration and
proliferation in **corneal** epithelial wound healing after
stimulation with either hepatocyte growth factor or keratinocyte growth
factor)

IT Eye

(cornea, epithelium; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Eye, disease
(cornea, injury; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Epithelium
Injury
(corneal; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Cell nucleus
(localization of p38 and ERK1/2; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Phosphorylation, biological
(of p38 and ERK1/2; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Cell migration
Cell proliferation
Epithelium
Signal transduction, biological
Wound healing
(p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT Hepatocyte growth factor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT 289898-51-7, JNK1 kinase 289899-93-0, JNK2 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(not involved; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT 137632-07-6, Protein kinase ERK1 137632-08-7, Protein kinase ERK2
148348-15-6, Fibroblast growth factor 7 165245-96-5, p38
Mitogen-activated protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

IT 289898-51-7, JNK1 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(not involved; p38 and ERK1/2 coordinate cellular migration and proliferation in corneal epithelial wound healing after stimulation with either hepatocyte growth factor or keratinocyte growth factor)

RN 289898-51-7 HCAPLUS
CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA

INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 7 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 12

ACCESSION NUMBER: 2003:886027 HCAPLUS

DOCUMENT NUMBER: 140:74225

TITLE: Discrete functions of TRAF1 and TRAF2 in Drosophila
melanogaster mediated by c-Jun

N-terminal kinase and
NF- κ B-dependent signaling pathways

AUTHOR(S): Cha, Guang-ho; Cho, Kyoung Sang; Lee, Jun Hee; Kim,
Myungjin; Kim, Euysoo; Park, Jeehye; Lee, Sung Bae;
Chung, Jongkyeong

CORPORATE SOURCE: National Creative Research Initiatives Center for Cell
Growth Regulation and Department of Biological
Sciences, Korea Advanced Institute of Science and
Technology, Taejon, 305-701, S. Korea

SOURCE: Molecular and Cellular Biology (2003), 23(22),
7982-7991

CODEN: MCEBD4; ISSN: 0270-7306

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 12 Nov 2003

AB Two Drosophila tumor necrosis factor receptor-associated factors (TRAF),
DTRAF1 and DTRAF2, are proposed to have similar functions with their
mammalian counterparts as a signal mediator of cell surface receptors.
However, their in vivo functions and related signaling pathways are not
fully understood yet. Here, we show that DTRAF1 is an in vivo regulator
of **c-Jun N-terminal kinase**
(JNK) pathway in D. melanogaster. Ectopic expression of DTRAF1 in the
developing **eye** induced apoptosis, thereby causing a rough-
eye phenotype. Further genetic interaction analyses revealed that
the apoptosis in the **eye** imaginal disk and the abnormal
eye morphogenesis induced by DTRAF1 are dependent on JNK and its
upstream kinases, Hep and DTAK1. In support of these results, DTRAF1-null
mutant showed a remarkable reduction in JNK activity with an impaired
development of imaginal disks and a defective formation of photosensory
neuron arrays. In contrast, DTRAF2 was demonstrated as an upstream
activator of nuclear factor- κ B (NF- κ B). Ectopic expression of
DTRAF2 induced nuclear translocation of 2 Drosophila NF- κ Bs, DIF and
Relish, consequently activating the transcription of the antimicrobial
peptide genes dipterecin, dipterecin-like protein, and drosomycin.
Consistently, the null mutant of DTRAF2 showed immune deficiencies in
which NF- κ B nuclear translocation and antimicrobial gene
transcription against microbial infection were severely impaired.
Collectively, our findings demonstrate that DTRAF1 and DTRAF2 play pivotal
roles in Drosophila development and innate immunity by differentially
regulating the JNK- and the NF- κ B-dependent signaling pathway, resp.

CC 12-3 (Nonmammalian Biochemistry)

IT Transcription factors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DIF; functions of TRAF1 and TRAF2 in Drosophila mediated by c-
-Jun N-terminal kinase and
NF- κ B-dependent signaling pathways in development)

IT Transcription factors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

- (NF- κ B (nuclear factor of κ light chain gene enhancer in B-cells); functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (Relish; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (TRAF1 (tumor necrosis factor receptor-associated factor 1); functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (TRAF2 (tumor necrosis factor receptor-associated factor 2); functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Peptides, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (antimicrobial; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (dipteracin-like; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Apoptosis
Cell nucleus
Cytoplasm
Development, nonmammalian postembryonic
Drosophila melanogaster
Eye
Signal transduction, biological
(functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Animal tissue
(imaginal disk; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Biological transport
(intracellular; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT Antimicrobial agents
(peptide; functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)
- IT 155215-87-5, **c-Jun N-terminal kinase** 182970-24-7, Drosomycin 184654-51-1, Dipteracin
RL: BSU (Biological study, unclassified); BIOL (Biological study) (functions of TRAF1 and TRAF2 in Drosophila mediated by **c-Jun N-terminal kinase** and NF- κ B-dependent signaling pathways in development)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 8 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 13

ACCESSION NUMBER: 2003:824892 HCAPLUS

DOCUMENT NUMBER: 140:24649

TITLE: Groucho suppresses Pax2 transactivation by inhibition of JNK-mediated phosphorylation

AUTHOR(S): Cai, Yi; Brophy, Patrick D.; Levitan, Inna; Stifani, Stefano; Dressler, Gregory R.

CORPORATE SOURCE: Department of Pathology and Pediatrics, University of Michigan, Ann Arbor, MI, 48109, USA

SOURCE: EMBO Journal (2003), 22(20), 5522-5529

CODEN: EMJODG; ISSN: 0261-4189

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 21 Oct 2003

AB Pax proteins are DNA-binding transcription factors that regulate embryonic development through the activation and repression of downstream target genes. The Pax2 gene is absolutely required for kidney development and for patterning specific regions of the nervous system such as the eye, ear and hindbrain. The Pax2/5/8 family of proteins contains both transcription activation and repression domains. The activation domain of Pax2 is phosphorylated by the c-Jun N-terminal kinase (JNK) to enhance Pax2-dependent transcription. In this report, we demonstrate that the Groucho/TLE family protein, Grg4, interacts with Pax2 to suppress transactivation. Grg4 is able to specifically inhibit phosphorylation of the Pax2 activation domain, even in the presence of activated JNK. Furthermore, the Grg4 interaction and suppression of phosphorylation depends on Pax2 binding to its target DNA sequence and is independent of histone deacetylation. These data suggest a new model for Groucho mediated suppression of transcription through the specific inhibition of modifications in the activation domain of a transactivator.

CC 6-3 (General Biochemistry)

Section cross-reference(s): 3

IT 289898-51-7, c-Jun N-terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (the groucho/TLE family protein Grg4 suppresses transactivation of Pax2 by inhibiting JNK-mediated phosphorylation of the Pax2 activation domain)

IT 289898-51-7, c-Jun N-terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (the groucho/TLE family protein Grg4 suppresses transactivation of Pax2 by inhibiting JNK-mediated phosphorylation of the Pax2 activation domain)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 9 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 2003:524757 HCAPLUS

DOCUMENT NUMBER: 139:195130

TITLE: JNK phosphorylates paxillin and regulates cell migration

AUTHOR(S): Huang, Cai; Rajfur, Zenon; Borchers, Christoph; Schaller, Michael D.; Jacobson, Ken

CORPORATE SOURCE: USA

SOURCE: Nature (London, United Kingdom) (2003), 424(6945), 219-223
CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 10 Jul 2003

AB The c-Jun amino-terminal kinase (JNK) is generally thought to be involved in inflammation, proliferation and apoptosis. Accordingly, its substrates are transcription factors and anti-apoptotic proteins. However, JNK has also been shown to be required for *Drosophila* dorsal closure, and MAP kinase/ERK kinase kinase 1, an upstream kinase in the JNK pathway, has been shown to be essential for cell migration. Both results imply that JNK is important in cell migration. Here we show that **JNK1** is required for the rapid movement of both fish **keratocytes** and rat bladder tumor epithelial cells (NBT-II). Moreover, **JNK1** phosphorylates serine 178 on paxillin, a focal adhesion adaptor, both in vitro and in intact cells. NBT-II cells expressing the Ser 178 → Ala mutant of paxillin (PaxS178A) formed focal adhesions and exhibited the limited movement associated with such contacts in both single-cell-migration and wound-healing assays. In contrast, cells expressing wild-type paxillin moved rapidly and retained close contacts as the predominant adhesion. Expression of PaxS178A also inhibited the migration of two other cell lines. Thus, phosphorylation of paxillin by JNK seems essential for maintaining the labile adhesions required for rapid cell migration.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 12

IT Adhesion, biological
Cell migration
Human
(MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish **keratocytes**, rat bladder tumor epithelial cells and human cell lines)

IT Paxillin (protein)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish **keratocytes**, rat bladder tumor epithelial cells and human cell lines)

IT Epithelium
(bladder; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish **keratocytes**, rat bladder tumor epithelial cells and human cell lines)

IT Bladder
(epithelium; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish **keratocytes**, rat bladder tumor epithelial cells and human cell lines)

IT Eye
(**keratocyte**; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish **keratocytes**, rat bladder tumor epithelial cells and human cell lines)

IT Protein motifs
(phosphorylation site, of paxillin; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish

keratocytes, rat bladder tumor epithelial cells and human cell lines)

IT Phosphorylation, biological
(protein; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish keratocytes, rat bladder tumor epithelial cells and human cell lines)

IT 289898-51-7, JNK1 protein kinase
335605-46-4, MKK7 kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish keratocytes, rat bladder tumor epithelial cells and human cell lines)

IT 56-45-1, L-Serine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Ser178, of paxillin; MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish keratocytes, rat bladder tumor epithelial cells and human cell lines)

IT 289898-51-7, JNK1 protein kinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(MKK7-activated JNK phosphorylates paxillin and regulates cell adhesion and migration of fish keratocytes, rat bladder tumor epithelial cells and human cell lines)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 10 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:962259 HCAPLUS

TITLE: Preparation of 4-substituted piperidine derivatives as Rho kinase antagonists

INVENTOR(S): McKerracher, Lisa; Thouin, Eryk; Lubell, William D.; Snow, Robert A.; Gingras, Karine

PATENT ASSIGNEE(S): Bioaxone Therapeutique Inc., Can.

SOURCE: PCT Int. Appl., 201 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005080394	A1	20050901	WO 2005-CA258	20050223
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: US 2004-546936P P 20040224

ED Entered STN: 02 Sep 2005

AB Title compds. I [A = C, N; q = 1 when A = C and 0 when A = N; p = 0-1; X = C, S with provisions; n = 0-1; R1-8 = H, alkyl, cycloalkyl, etc.; R9-10 = H, alkyl, cycloalkyl, etc.; R11-12 = H, aryl, alkyl, cycloalkyl, etc.] are prepared. Examples include synthetic details for several compds.' synthesis, ROCK-II kinase (as well as other kinase substrates) activity and a neurite outgrowth assay. For instance, II is prepared in 8 steps from 1-(benzyloxycarbonyl)-4-formylpiperidine (preparation given), methylmagnesium bromide, sodium azide and 5-isoquinoline sulfonyl chloride. II has IC50 = 791 nM for ROCK-II kinase. I may induce the regeneration or growth of neurites in mammalian nerve cells and may thereby induce regeneration of damaged or diseased nerve tissue. These compds. also find addnl. utility as antagonists of the enzyme Rho kinase in treatment of disease states in which Rho kinase is implicated.

IC ICM C07D473-00
ICS C07D401-12; C07D401-14; C07D471-04; C07D211-56; C07D211-60;
C07D211-96; A61K031-4545; A61K031-4725; A61K031-445; A61P035-00;
A61P025-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

IT **Eye, disease**
(macula, degeneration; preparation of 4-substituted piperidine derivs. as Rho kinase antagonists)

IT 137632-08-7, Protein kinase MAPK1 141436-78-4, Protein kinase Cα 144697-17-6, Tyrosine kinase c-Src 156621-09-9, MSK-1 protein kinase 182372-13-0, Rho kinase 182938-07-4, ROCK I kinase 182938-08-5, ROCK-II protein kinase 185156-08-5, Protein kinase PRK2 194812-12-9, TRK-E protein tyrosine kinase 289898-51-7, **JNK1 kinase** 391208-93-8, Protein kinase GSK3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 4-substituted piperidine derivs. as Rho kinase antagonists)

IT 289898-51-7, **JNK1 kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of 4-substituted piperidine derivs. as Rho kinase antagonists)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 11 OF 79 HCAPLUS - COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:902703 HCAPLUS

TITLE: Gene expression profiles in the diagnosis and treatment of Alzheimer's disease

INVENTOR(S): Landfield, Philip W.; Porter, Nada M.; Chen, Kuey Chu; Geddes, James; Blalock, Eric

PATENT ASSIGNEE(S): University of Kentucky Research Foundation, USA

SOURCE: PCT Int. Appl., 114 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005076939	A2	20050825	WO 2005-US3668	20050209
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
 RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
 MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2004-542281P

P 20040209

ED Entered STN: 26 Aug 2005

AB Genes showing altered patterns of expression in the brain that are associated with the neurol. changes found in Alzheimer's disease and that can be used in the early diagnosis of the disease, including the incipient form of the disease, are identified. The methods and kits of the invention utilize a set of genes and their encoded proteins that are shown to be correlated with incipient Alzheimer's disease.

IC ICM C12N

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 15

L640 ANSWER 12 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:612106 HCAPLUS

DOCUMENT NUMBER: 143:109792

TITLE: Methods and compositions using a glutathione donor with other agents for the prevention and treatment of inflammatory diseases or conditions

INVENTOR(S): Singh, Inderjit

PATENT ASSIGNEE(S): Musc Foundaton for Research Development, USA

SOURCE: PCT Int. Appl., 106 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005063275	A1	20050714	WO 2004-US43432	20041223
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

US 2003-531828P

P 20031223

US 2004-559112P

P 20040402

ED Entered STN: 15 Jul 2005

AB The invention discloses methods and compns. for treating or preventing inflammatory diseases or conditions in a patient, comprising administering to the patient a therapeutically effective amount of a composition comprising a glutathione donor, 5-amino 4-imidazolecarboxamide ribotide (AICAR), an HMG-CoA reductase inhibitor, D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol HCl (D-PDMP), and/or 1,5-(butylimino)-1,5-dideoxy-D-glucitol (Miglustat), or derivs. thereof.

IC ICM A61K038-00
 CC 1-7 (Pharmacology)
 Section cross-reference(s): 63
 IT **Eye, disease**
 Inflammation
 (ophthalmitis; glutathione donor with other agents for
 prevention and treatment of inflammatory diseases or conditions)
 IT 57-88-5, Cholesterol, biological studies 70-18-8, Glutathione,
 biological studies 4682-48-8, Lactosylceramide 9023-93-2, Acetyl-CoA
 carboxylase 10102-43-9, Nitric oxide, biological studies 37758-47-7,
 Ganglioside GM1 54827-14-4, Ganglioside GM3 59298-90-7,
 Lactosylceramide synthase 62010-37-1, Ganglioside GD3 72060-33-4,
 Amp-activated protein kinase kinase 85305-87-9, Glucosylceramide
 85305-88-0, Galactosylceramide 125978-95-2, Nitric oxide synthase
 137632-07-6, Erk1 kinase 137632-08-7, Erk2 kinase 165245-96-5, p38 Map
 kinase 172522-01-9, Amp-activated protein kinase 289898-51-7,
Jnk1 kinase 289899-93-0, Jnk2 kinase 362516-16-3,
 Protein kinase IKK α 362517-43-9, IKK β kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (glutathione donor with other agents for prevention and treatment of
 inflammatory diseases or conditions)
 IT **289898-51-7, Jnk1 kinase**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (glutathione donor with other agents for prevention and treatment of
 inflammatory diseases or conditions)
 RN 289898-51-7 HCAPLUS
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 13 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:447673 HCAPLUS

DOCUMENT NUMBER: 143:20875

TITLE: Differentially expressed gene profile for diagnosing
 and treating mental disorders

INVENTOR(S): Akil, Huda; Atz, Mary; Bunney, William E., Jr.;
 Choudary, Prabhakara V.; Evans, Simon J.; Jones,
 Edward G.; Li, Jun; Lopez, Juan F.; Myers, Richard;
 Thompson, Robert C.; Tomita, Hiroaki; Vawter, Marquis
 P.; Watson, Stanley

PATENT ASSIGNEE(S): The Board of Trustees of the Leland Stanford Junior
 University, USA

SOURCE: PCT Int. Appl., 226 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005046434	A2	20050526	WO 2004-US36784	20041105
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,			

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO,
 SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
 NE, SN, TD, TG

US 2005209181 A1 20050922 US 2004-982556 20041104
 PRIORITY APPLN. INFO.: US 2003-517751P P 20031105
 US 2004-982556 A 20041104

ED Entered STN: 26 May 2005

AB The present invention provides methods for diagnosing mental disorders (e.g., psychotic disorders such as schizophrenia). The present invention uses DNA microarray anal. to demonstrate differential expression of genes in selected regions of post-mortem brains from patients diagnosed with mental disorders in comparison with normal control subjects. The invention also provides methods of identifying modulators of such mental disorders as well as methods of using these modulators to treat patients suffering from such mental disorders.

IC ICM A61B

CC 3-1 (Biochemical Genetics)

Section cross-reference(s): 1, 6, 7, 14

IT Proteins

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)

(JIP-2 (c-Jun N-terminal

kinase-interacting protein-2); compns. and DNA microarray assay for diagnosis, prognosis and therapy of mental disorders)

IT Transcription factors

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)

(MITF (microphthalmia-associated transcription factor); compns.

and DNA microarray assay for diagnosis, prognosis and therapy of mental disorders)

L640 ANSWER 14 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:141054 HCAPLUS

DOCUMENT NUMBER: 142:240431

TITLE: Preparation of isoquinoline derivatives as c
 -Jun N-terminal
 kinase (JNK) inhibitors

INVENTOR(S): Kitamura, Shuji; Kajino, Masahiro; Asano, Yasutomi;
 Fukumoto, Shoji; Igata, Hideki

PATENT ASSIGNEE(S): Takeda Pharmaceutical Company Limited, Japan

SOURCE: PCT Int. Appl., 223 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005014576	A1	20050217	WO 2004-JP11738	20040810
WO 2005014576	C1	20050519		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
 AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
 EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
 SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
 SN, TD, TG

PRIORITY APPLN. INFO.: JP 2003-207417 A 20030812
 JP 2004-167856 A 20040604

OTHER SOURCE(S): MARPAT 142:240431

ED Entered STN: 18 Feb 2005

AB 4-Phenyl-1,2-dihydroisoquinolin-1-one derivs. (I) [ring A and B =
 (un)substituted benzene ring; R1 = (un)substituted aromatic heterocyclyl; R2
 = acyl], or salts thereof are prepared There is provided a
 preventive/therapeutic agent for JNK-associated pathol. condition or disorder
 that exhibits excellent JNK-specific inhibitory activity and excellent
 oral absorption. JNK-associated pathol. conditions or disorders include
 chronic or acute heart failure, cardiac hypertrophy, cardiomyopathy, acute
 myocardial infarction, acute or chronic myocarditis, left ventricular
 expansion or contraction failure, hypertension, nephropathy or nephritis
 combined with hypertension, lowered function of vascular endothelial,
 arteriosclerosis, restenosis after coronary angioplasty, chronic articular
 rheumatism, osteoarthritis, gout, chronic obstructive lung diseases,
 asthma, bronchitis, cystic fibrosis, inflammatory bowel disease, irritable
 bowel syndrome, mucosal colitis, ulcerative colitis, Crohn's disease,
 gastritis, esophagus infection, multiple sclerosis, eczema, dermatitis,
 hepatitis, glomerulonephritis, allergy, diabetes, diabetic nephritis,
 diabetic retinopathy, diabetic neuropathy, obesity, psoriasis, cancer,
 Alzheimer's disease, Huntington chorea, parkinson's disease, epilepsy,
 amyotrophic lateral sclerosis, peripheral nerve disorder, spinal cord
 injury, stroke, cerebral vascular disorders, ischemic disorders of organs
 such as heart, kidney, liver, or brain, ischemic reperfusion disorder,
 organ failure, endotoxin shock, and transplant rejection. Thus,
 chlorination of 2-benzoyl-4-chlorobenzoic acid with SOCl₂ in the presence
 of DMF in toluene at 60° followed by amidation with
 5-[(2-hydroxybutyl)amino]methyl-1H-pyrazole-3-carboxylic acid Et ester
 in the presence of N-ethyldiisopropylamine in toluene at 90° for 2
 h, and oxidation with SO₃-pyridine complex in the presence of Et₃N in DMSO at
 room temperature for 2 h, and cyclization using 1,8-diazabicyclo[5.4.0]-7-
 undecene in a mixture of ethanol, MeOH, and THF under refluxing for 12 h
 gave 25% 3-[(6-chloro-1-oxo-4-phenyl-3-propionyl-2(1H)-
 isoquinolinyl)methyl]-1H-pyrazole-5-carboxylic acid Et ester which was
 converted into 3-[(6-chloro-1-oxo-4-phenyl-3-propionyl-2(1H)-
 isoquinolinyl)methyl]-1-methyl-1H-pyrazole-5-carboxamide (II) by
 methylation with Me iodide, saponification, and amidation with ammonia. II at

10

μM inhibited human JNK1 by >95%. Pharmaceutical
 formulations, e.g. a capsule formulation containing II, were described.

IC ICM C07D401-06

ICS C07D401-14; C07D405-14; C07D413-06; C07D417-14; A61K031-4725;
 A61K031-5377; A61K031-5355; A61P001-04; A61P001-16; A61P003-04;
 A61P003-10; A61P009-00; A61P009-04; A61P009-10; A61P009-12;
 A61P011-00; A61P011-06; A61P013-00; A61P017-00

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1, 7, 63

ST isoquinolinylmethylpyrazolecarboxamide prepn JNK inhibitor; isoquinoline
 prepn c Jun N terminal
 kinase inhibitor; heart failure treatment isoquinoline prepn;
 cardiac hypertrophy treatment isoquinoline prepn; cardiomyopathy treatment
 isoquinoline prepn; acute myocardial infarction treatment isoquinoline
 prepn; chronic myocarditis treatment isoquinoline prepn;
 phenyldihydroisoquinolinone prepn JNK inhibitor

- IT Inflammation
(Crohn's disease; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Intestine, disease
(Crohn's; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Nervous system, disease
(Huntington's chorea; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Nervous system, disease
(amyotrophic lateral sclerosis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Bronchi, disease
Inflammation
(bronchitis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Hypertrophy
Ischemia
(cardiac; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart, disease
(cardiomyopathy; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Ischemia
(cerebral; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Brain, disease
(cerebrovascular; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Lung, disease
(chronic obstructive; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Inflammation
Intestine, disease
(colitis, mucosal colitis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Artery, disease
(coronary, restenosis, after coronary angioplasty; preparation of

isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)

- IT Kidney, disease
(diabetic nephropathy; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Nerve, disease
(diabetic neuropathy; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Eye, disease
(diabetic retinopathy; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart, disease
Organ, animal, disease
(failure; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Inflammation
Stomach, disease
(gastritis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Inflammation
Kidney, disease
(glomerulonephritis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Ischemia
(hepatic; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart, disease
(hypertrophy; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart, disease
(infarction; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Esophagus
(infection; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Intestine, disease
(inflammatory; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK)

- inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Spinal cord, disease
(injury; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Intestine, disease
(irritable bowel syndrome; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Brain, disease
Heart, disease
Kidney, disease
Liver, disease
(ischemia; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Reperfusion
(ischemic reperfusion; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart
(left ventricle, left ventricular expansion or contraction failure; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Blood vessel, disease
(lowered function of vascular endothelial; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Heart, disease
Inflammation
(myocarditis; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Nerve
(peripheral, diseases; preparation of isoquinoline derivs. as **c-Jun N-terminal kinase** (JNK) inhibitors and preventives and/or therapeutic agents for JNK-associated pathol. conditions or disorders)
- IT Allergy
Allergy inhibitors
Alzheimer's disease
Anti-Alzheimer's agents
Anti-ischemic agents
Antiartherosclerotics
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antihypertensives
Antiobesity agents
Antiparkinsonian agents
Antirheumatic agents

Antitumor agents
 Arteriosclerosis
 Asthma
 Cystic fibrosis
 Dermatitis
 Diabetes mellitus
 Eczema
 Epilepsy
 Gout
 Hepatitis
 Human
 Hypertension
 Ischemia
 Multiple sclerosis
 Neoplasm
 Obesity
 Osteoarthritis
 Parkinson's disease
 Psoriasis
 Rheumatoid arthritis
 Transplant rejection
 (preparation of isoquinoline derivs. as **c-Jun N**
 -terminal kinase (JNK) inhibitors and preventives
 and/or therapeutic agents for JNK-associated pathol. conditions or
 disorders)
 IT Ischemia
 (renal; preparation of isoquinoline derivs. as **c-Jun**
 N-terminal kinase (JNK) inhibitors and
 preventives and/or therapeutic agents for JNK-associated pathol.
 conditions or disorders)
 IT Shock (circulatory collapse)
 (septic; preparation of isoquinoline derivs. as **c-Jun**
 N-terminal kinase (JNK) inhibitors and
 preventives and/or therapeutic agents for JNK-associated pathol.
 conditions or disorders)
 IT Injury
 (spinal cord; preparation of isoquinoline derivs. as **c-Jun**
 N-terminal kinase (JNK) inhibitors and
 preventives and/or therapeutic agents for JNK-associated pathol.
 conditions or disorders)
 IT Brain, disease
 (stroke; preparation of isoquinoline derivs. as **c-Jun**
 N-terminal kinase (JNK) inhibitors and
 preventives and/or therapeutic agents for JNK-associated pathol.
 conditions or disorders)
 IT Inflammation
 Intestine, disease
 (ulcerative colitis; preparation of isoquinoline derivs. as **c-**
 Jun N-terminal kinase (JNK)
 inhibitors and preventives and/or therapeutic agents for JNK-associated
 pathol. conditions or disorders)
 IT 155215-87-5, **c-Jun N-terminal**
 kinase
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (human JNK 1; preparation of isoquinoline derivs. as **c-Jun**
 N-terminal kinase (JNK) inhibitors and
 preventives and/or therapeutic agents for JNK-associated pathol.
 conditions or disorders)
 IT 844869-80-3P 844869-81-4P 844869-83-6P 844869-86-9P 844869-87-0P
 844869-88-1P 844869-89-2P 844869-90-5P 844869-91-6P 844869-97-2P

844869-98-3P	844869-99-4P	844870-05-9P	844870-08-2P	844870-10-6P
844870-23-1P	844870-25-3P	844870-26-4P	844870-27-5P	844870-29-7P
844870-31-1P	844870-49-1P	844870-51-5P	844870-52-6P	844870-53-7P
844870-54-8P	844870-55-9P	844870-56-0P	844870-62-8P	844870-66-2P
844870-70-8P	844870-71-9P	844870-74-2P	844870-75-3P	844870-76-4P
844870-85-5P	844870-87-7P	844870-89-9P	844871-18-7P	844871-19-8P
844871-24-5P	844871-26-7P	844871-29-0P	844871-31-4P	844871-33-6P
844871-36-9P	844871-37-0P	844871-39-2P	844871-45-0P	844871-50-7P
844871-57-4P	844871-59-6P	844871-69-8P	844871-70-1P	844871-74-5P
844871-75-6P	844871-79-0P	844871-82-5P	844871-85-8P	844871-88-1P
844871-91-6P	844871-93-8P	844872-00-0P	844872-01-1P	844872-06-6P
844872-13-5P	844872-18-0P	844872-19-1P	844872-20-4P	

RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of isoquinoline derivs. as c-Jun N

-terminal kinase (JNK) inhibitors and preventives

and/or therapeutic agents for JNK-associated pathol. conditions or disorders)

IT	844869-82-5P	844869-84-7P	844869-85-8P	844869-92-7P	844869-93-8P
	844869-94-9P	844869-95-0P	844869-96-1P	844870-00-4P	844870-01-5P
	844870-02-6P	844870-03-7P	844870-04-8P	844870-07-1P	844870-09-3P
	844870-11-7P	844870-12-8P	844870-13-9P	844870-14-0P	844870-15-1P
	844870-16-2P	844870-17-3P	844870-18-4P	844870-19-5P	844870-20-8P
	844870-22-0P	844870-24-2P	844870-28-6P	844870-30-0P	844870-32-2P
	844870-33-3P	844870-34-4P	844870-35-5P	844870-36-6P	844870-37-7P
	844870-38-8P	844870-39-9P	844870-40-2P	844870-41-3P	844870-43-5P
	844870-44-6P	844870-45-7P	844870-46-8P	844870-47-9P	844870-48-0P
	844870-50-4P	844870-57-1P	844870-58-2P	844870-59-3P	844870-60-6P
	844870-61-7P	844870-63-9P	844870-64-0P	844870-65-1P	844870-67-3P
	844870-68-4P	844870-69-5P	844870-72-0P	844870-73-1P	844870-77-5P
	844870-78-6P	844870-79-7P	844870-80-0P	844870-81-1P	844870-83-3P
	844870-90-2P	844870-92-4P	844870-94-6P	844870-96-8P	844870-98-0P
	844871-00-7P	844871-01-8P	844871-03-0P	844871-04-1P	844871-06-3P
	844871-07-4P	844871-08-5P	844871-09-6P	844871-10-9P	844871-11-0P
	844871-12-1P	844871-13-2P	844871-14-3P	844871-15-4P	844871-16-5P
	844871-17-6P	844871-20-1P	844871-21-2P	844871-22-3P	844871-23-4P
	844871-25-6P	844871-27-8P	844871-28-9P	844871-30-3P	844871-32-5P
	844871-34-7P	844871-35-8P	844871-38-1P	844871-40-5P	844871-41-6P
	844871-42-7P	844871-43-8P	844871-44-9P	844871-46-1P	844871-47-2P
	844871-48-3P	844871-49-4P	844871-51-8P	844871-52-9P	844871-53-0P
	844871-54-1P	844871-55-2P	844871-56-3P	844871-58-5P	844871-60-9P
	844871-61-0P	844871-62-1P	844871-63-2P	844871-64-3P	844871-65-4P
	844871-66-5P	844871-67-6P	844871-68-7P	844871-71-2P	844871-72-3P
	844871-73-4P	844871-76-7P	844871-77-8P	844871-78-9P	844871-80-3P
	844871-81-4P	844871-83-6P	844871-84-7P	844871-86-9P	844871-87-0P
	844871-89-2P	844871-90-5P	844871-92-7P	844871-94-9P	844871-95-0P
	844871-96-1P	844871-97-2P	844871-98-3P	844871-99-4P	844872-02-2P
	844872-03-3P	844872-04-4P	844872-05-5P	844872-07-7P	844872-08-8P
	844872-09-9P	844872-10-2P	844872-11-3P	844872-12-4P	844872-15-7P
	844872-16-8P	844872-17-9P	844872-22-6P	844872-24-8P	844872-25-9P
	844872-26-0P	844872-27-1P	844872-28-2P	844873-48-9P	845259-84-9P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoquinoline derivs. as c-Jun N

-terminal kinase (JNK) inhibitors and preventives

and/or therapeutic agents for JNK-associated pathol. conditions or disorders)

IT 74-88-4, Methyl iodide, reactions 74-89-5, Methylamine, reactions

75-03-6, Ethyl iodide 75-04-7, Ethylamine, reactions 75-16-1,
 Methylmagnesium bromide 75-30-9, 2-Iodopropane 75-64-9,
 tert-Butylamine, reactions 76-83-5, Trityl chloride 78-83-1, Isobutyl
 alcohol, reactions 78-92-2, sec-Butanol 78-95-5, Chloroacetone
 105-36-2, Ethyl bromoacetate 108-24-7, Acetic anhydride 109-89-7,
 Diethylamine, reactions 109-90-0, Ethyl isocyanate 118-45-6,
 4-Chlorophthalic anhydride 124-40-3, Dimethylamine, reactions
 124-63-0, Methanesulfonyl chloride 126-30-7, 2,2-Dimethylpropane-1,3-
 diol 359-13-7, 2,2-Difluoroethanol 430-67-1, 2,2-Difluoroethylamine
 462-06-6, Fluorobenzene 540-51-2, 2-Bromoethanol 556-52-5,
 Oxiran-2-ylmethanol 584-13-4, [1,2,4]Triazol-4-ylamine 615-79-2,
 2,4-Dioxopentanoic acid ethyl ester 624-83-9, Methyl isocyanate
 765-30-0, Cyclopropylamine 920-39-8, Isopropylmagnesium bromide
 1068-57-1, Acetohydrazide 2568-33-4, 3-Methylbutane-1,3-diol
 3034-50-2, 4-Formylimidazole 3099-31-8 3143-02-0, (3-Methyloxetan-3-
 yl)methanol 3469-69-0, 4-Iodopyrazole 3920-50-1, 3-Formylpyrazole
 5042-30-8 5188-07-8, Sodium thiomethoxide 5292-43-3, tert-Butyl
 bromoacetate 5343-35-1, 1-Aminopentane-2-ol 5470-11-1 5680-79-5
 6342-56-9, 1,1-Dimethoxyacetone 6482-24-2, 1-Bromo-2-methoxyethane
 6638-79-5, N,O-Dimethylhydroxylamine hydrochloride 7400-27-3, tert-Butyl
 hydrazine hydrochloride 7677-24-9, Trimethylsilyl cyanide 7803-57-8,
 Hydrazine hydrate 13552-21-1, 1-Aminobutan-2-ol 13831-31-7
 17739-45-6, 2-(2-Bromoethoxy)tetrahydro-2H-pyran 17969-22-1,
 4-Chloromethyl-2-(4-chlorophenyl)thiazole 22103-85-1, 2-Benzoylbenzoyl
 chloride 24424-99-5, Di-tert-butyl dicarbonate 26690-80-2,
 (2-Hydroxyethyl)carbamic acid tert-butyl ester 26734-09-8,
 3-Amino-2,2-dimethylpropan-1-ol 32300-55-3 33184-56-4,
 2-Benzoyl-4-chlorobenzoic acid 35034-22-1, 2-Methyl-4-formylimidazole
 70258-18-3, 2-Chloro-5-(chloromethyl)pyridine 75436-40-7 100960-16-5
 102229-10-7, 2-(tert-Butyldimethylsilyloxy)ethanol 198348-89-9,
 5-Nitro-1H-pyrazole-3-carboxylic acid 357333-09-6 412299-83-3,
 2-Benzoyl-4-bromobenzoic acid 844872-60-2 844872-83-9

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of isoquinoline derivs. as c-Jun N
 -terminal kinase (JNK) inhibitors and preventives
 and/or therapeutic agents for JNK-associated pathol. conditions or
 disorders)

IT 3209-72-1P, 5-Methylisoxazole-3-carboxylic acid ethyl ester 4027-57-0P,
 5-Methyl-1H-pyrazole-3-carboxylic acid ethyl ester 22667-24-9P
 33016-47-6P, 1-Trityl-1H-imidazole-4-carboxaldehyde 89239-82-7P
 93290-12-1P 129490-25-1P, 2-Methyl-1-trityl-1H-imidazole-4-
 carboxaldehyde 132844-48-5P 175277-08-4P 191017-09-1P 191980-54-8P
 213764-25-1P 218594-00-4P 568596-63-4P 569657-29-0P 569657-30-3P
 844872-29-3P 844872-30-6P 844872-31-7P 844872-32-8P 844872-33-9P
 844872-34-0P 844872-35-1P 844872-36-2P 844872-37-3P 844872-38-4P
 844872-39-5P 844872-41-9P 844872-43-1P 844872-44-2P 844872-46-4P
 844872-48-6P 844872-49-7P 844872-51-1P 844872-54-4P 844872-57-7P
 844872-59-9P 844872-61-3P 844872-62-4P 844872-63-5P 844872-64-6P
 844872-65-7P 844872-66-8P 844872-68-0P 844872-69-1P 844872-70-4P
 844872-71-5P 844872-72-6P 844872-73-7P 844872-74-8P 844872-75-9P
 844872-76-0P 844872-77-1P 844872-78-2P 844872-79-3P 844872-80-6P
 844872-81-7P 844872-82-8P 844872-84-0P 844872-85-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(preparation of isoquinoline derivs. as c-Jun N
 -terminal kinase (JNK) inhibitors and preventives
 and/or therapeutic agents for JNK-associated pathol. conditions or
 disorders)

IT 845471-03-6 845471-04-7 845471-05-8 845471-06-9 845471-07-0
 845471-08-1 845471-09-2 845471-10-5

RL: PRP (Properties)
 (unclaimed nucleotide sequence; preparation of isoquinoline derivs. as
c-Jun N-terminal kinase
 (JNK) inhibitors)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 15 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:394682 HCAPLUS

DOCUMENT NUMBER: 142:445550

TITLE: Gene expression profiles for the diagnosis and
 prognosis of breast cancer

INVENTOR(S): Erlander, Mark; Ma, Xiao-Jun; Wang, Wei; Wittliff,
 James L.

PATENT ASSIGNEE(S): Arcturus Bioscience, Inc. University of Louisville,
 USA

SOURCE: U.S. Pat. Appl. Publ., 40 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005095607	A1	20050505	US 2004-795092	20040305
PRIORITY APPLN. INFO.:			US 2003-453006P	P 20030307

ED Entered STN: 09 May 2005

AB The invention relates to the identification and use of gene expression
 profiles, or patterns, suitable for identification of breast cancer
 patient populations with different survival outcomes. The gene expression
 profiles may be embodied in nucleic acid expression, protein expression,
 or other expression formats, and may be used in the study and/or determination
 of the prognosis of a patient, including breast cancer survival.

IC ICM C12Q001-68

INCL 435006000

CC 14-1 (Mammalian Pathological Biochemistry)

Section cross-reference(s): 3

IT Gene, **animal**

RL: ANT (Analyte); BSU (Biological study, unclassified); DGN (Diagnostic
 use); PRP (Properties); ANST (Analytical study); BIOL (Biological study);
 USES (Uses)

(COR01C, in breast cancer diagnosis; gene expression profiles for
 diagnosis and prognosis of breast cancer)

IT Proteins

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP
 (Properties); BIOL (Biological study); USES (Uses)

(JIP-2 (**c-Jun N-terminal**
kinase-interacting protein-2), gene for, in breast cancer
 diagnosis; gene expression profiles for diagnosis and prognosis of
 breast cancer)

L640 ANSWER 16 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:99129 HCAPLUS

DOCUMENT NUMBER: 142:149139

TITLE: Feline proinsulin, insulin, constituent peptides, and
 peptidomimetics in the treatment of diabetes and
 associated disorders and for diagnosis

INVENTOR(S): Hoenig, Margarethe

PATENT ASSIGNEE(S): USA
 SOURCE: U.S. Pat. Appl. Publ., 33 pp.
 CODEN: USXXCO
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005026826	A1	20050203	US 2004-760928	20040120
PRIORITY APPLN. INFO.:			US 2003-440964P	P 20030117
			US 2003-444009P	P 20030131

ED Entered STN: 04 Feb 2005

AB The amino acid sequences of feline proinsulin and structurally related polypeptides such as insulin and the A, B and C chains are provided. Also provided are peptidomimetics, analogs, polypeptide subunits, polynucleotides that encode the polypeptides and subunits thereof, methods of making the polypeptides and polynucleotides, antibodies, peptide aptamers, and diagnostic and therapeutic methods. A method to identify an antiproliferative factor comprising: incubating neuroblastoma test cells with feline C-peptide, insulin, and a candidate antiproliferative factor is also claimed. Kits comprising packaging material and a first antibody that specifically binds to a feline C-peptide, and a second antibody that specifically binds to feline insulin are also claimed.

IC ICM A61K038-17

ICS C07K007-08

INCL 514012000; 530324000

CC 2-6 (Mammalian Hormones)

Section cross-reference(s): 3

IT **Eye, disease**

(diabetic retinopathy; feline proinsulin, insulin, constituent peptides, and peptidomimetics in treatment of diabetes and associated disorders and for diagnosis)

IT Phosphorylation, biological

(protein, reduction of c-jun N-terminal kinase phosphorylation; feline proinsulin, insulin, constituent peptides, and peptidomimetics in treatment of diabetes and associated disorders and for diagnosis)

IT 155215-87-5, c-Jun N-terminal kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (reduction of c-jun N-terminal

kinase phosphorylation; feline proinsulin, insulin, constituent peptides, and peptidomimetics in treatment of diabetes and associated disorders and for diagnosis)

L640 ANSWER 17 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:671727 HCAPLUS

DOCUMENT NUMBER: 143:166667

TITLE: The curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs

INVENTOR(S): Ueno, Yuki; Tsuda, Takanori; Takanori, Hitoshi; Yoshikawa, Toshikazu; Osawa, Toshihiko

PATENT ASSIGNEE(S): Biomarker Science Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 85 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	JP 2005198640	A2	20050728	JP 2004-53258	20040227
PRIORITY APPLN. INFO.:				JP 2003-394758	A 20031125

ED Entered STN: 29 Jul 2005

AB The curcuminoids- and anthocyanins-responsive gene expression profiles in adipocytes have been revealed. The curcuminoids- and anthocyanins-responsive genes are designed to be used as the index markers in the screenings of the substances that can affect the gene expression patterns in obesity and diabetes. These substances can be the candidates of anti-obesity and anti-diabetes drugs. Therefore, the groups of curcuminoids- and anthocyanins-responsive genes are intended to be used as markers in a form of kit such as DNA chip for the screening of anti-obesity and anti-diabetes drugs.

IC ICM C12N005-02
ICS C12N015-09; C12Q001-68

CC 1-10 (Pharmacology)
Section cross-reference(s): 2, 3, 6, 7, 9, 14

IT Proteins
RL: BSU (Biological study, unclassified); BIOL (Biological study) (JIP-2 (**c-Jun N-terminal kinase**-interacting protein-2), gene for; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study) (MITF (**microphthalmia**-associated transcription factor), gene for; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

IT Antigens
RL: BSU (Biological study, unclassified); BIOL (Biological study) (autoantigens, La, **Sjogren** syndrome antigen B, gene for; curcuminoids- and anthocyanins-responsive genes in human adipocytes and their use in screenings of anti-obesity and anti-diabetes drugs)

L640 ANSWER 18 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:215845 HCAPLUS

DOCUMENT NUMBER: 142:298011

TITLE: Preparation of isoquinolinones and their use as selective **c-Jun N-terminal kinase** (JNK) inhibitors and (pro)drugs

INVENTOR(S): Fukumoto, Masashi; Asano, Yasuomi; Ikata, Hideki

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 219 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	JP 2005060247	A2	20050310	JP 2003-207418	20030812
PRIORITY APPLN. INFO.:				JP 2003-207418	20030812
OTHER SOURCE(S):			MARPAT 142:298011		

ED Entered STN: 11 Mar 2005

AB Title compds. I [ring A, B maybe substituted; X = divalent aliphatic hydrocarbylene; R1 = H, (un)substituted OH, (un)substituted SH, (un)substituted SO2, (un)substituted amino, acyl, cyano, (un)substituted nonarom. hydrocarbon ring, etc.; R2 = similar group as in R1 except H], useful for treatment of JNK-related diseases, e.g., heart failure, arteriosclerosis, rheumatoid arthritis, asthma, and Alzheimer's disease, are prepared Thus, treatment of 6-chloro-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-1-one with NaH and 2-(3-bromopropyl)isoindoline-1,3-dione gave 5% 2-[3-(6-chloro-1-oxo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-2-yl)propyl]isoindoline-1,3-dione, which at 10 μ M inhibited >90% human **JNK1**.

IC ICM C07D217-24

ICS A61K031-472; A61K031-4725; A61K031-496; A61K031-5377; A61K031-55; A61K031-551; A61P001-04; A61P001-16; A61P003-04; A61P003-10; A61P009-04; A61P009-10; A61P009-12; A61P011-06; A61P011-08; A61P013-12; A61P017-00; A61P017-06; A61P019-02

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

IT Inflammation
(Crohn's disease; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Intestine, disease
(Crohn's; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Nervous system, disease
(Huntington's chorea; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Nervous system, disease
(amyotrophic lateral sclerosis; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Bronchi, disease
Inflammation
(bronchitis; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Hypertrophy
Ischemia
(cardiac; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Heart, disease
(cardiomyopathy; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Ischemia
(cerebral; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Brain, disease
(cerebrovascular; preparation of isoquinolinones as selective c-**Jun N-terminal kinase** inhibitors and (pro)drugs)

IT Lung, disease
(chronic obstructive; preparation of isoquinolinones as selective c-**Jun N-terminal kinase**

inhibitors and (pro)drugs)

IT Inflammation
Intestine, disease
(colitis, mucous; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Artery, disease
(coronary, restenosis, after coronary angioplasty; preparation of
isoquinolinones as selective c-**Jun N-**
terminal kinase inhibitors and (pro)drugs)

IT Kidney, disease
(diabetic nephropathy; preparation of isoquinolinones as selective c
-**Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Nerve, disease
(diabetic neuropathy; preparation of isoquinolinones as selective c
-**Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Eye, disease
(diabetic retinopathy; preparation of isoquinolinones as
selective c-**Jun N-terminal**
kinase inhibitors and (pro)drugs)

IT Esophagus, disease
Inflammation
(esophagitis; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Heart, disease
(failure, acute; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Heart, disease
(failure, chronic; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Organ, animal, disease
(failure; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Inflammation
Stomach, disease
(gastritis; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Inflammation
Kidney, disease
(glomerulonephritis; preparation of isoquinolinones as selective c
-**Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Ischemia
(hepatic; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Heart, disease
(hypertrophy; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors
and (pro)drugs)

IT Kidney, disease
(in hypertension; preparation of isoquinolinones as selective c-
Jun N-terminal kinase inhibitors

and (pro)drugs)

IT Heart, disease
(infarction; preparation of isoquinolinones as selective **c-Jun N-terminal kinase** inhibitors
and (pro)drugs)

IT Intestine, disease
(inflammatory; preparation of isoquinolinones as selective **c-Jun N-terminal kinase** inhibitors
and (pro)drugs)

IT Spinal column
(injury; preparation of isoquinolinones as selective **c-Jun N-terminal kinase** inhibitors and
(pro)drugs)

IT Intestine, disease
(irritable bowel syndrome; preparation of isoquinolinones as selective **c-Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Brain, disease
Heart, disease
Kidney, disease
Liver, disease
(ischemia; preparation of isoquinolinones as selective **c-Jun N-terminal kinase** inhibitors
and (pro)drugs)

IT Heart
(left ventricle, disease; preparation of isoquinolinones as selective **c-Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Heart, disease
Inflammation
(myocarditis; preparation of isoquinolinones as selective **c-Jun N-terminal kinase** inhibitors
and (pro)drugs)

IT Inflammation
Kidney, disease
(nephritis, in hypertension; preparation of isoquinolinones as selective **c-Jun N-terminal kinase**
inhibitors and (pro)drugs)

IT Alzheimer's disease
Anti-Alzheimer's agents
Anti-ischemic agents
Antiartherosclerotics
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antihypertensives
Antiobesity agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Arteriosclerosis
Asthma
Cystic fibrosis
Dermatitis
Diabetes mellitus
Eczema
Epilepsy
Gout
Hepatitis
Human

Hypertension
Multiple sclerosis
Neoplasm
Obesity
Osteoarthritis
Parkinson's disease
Psoriasis
Rheumatoid arthritis
Transplant rejection

(preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
(pro)drugs)

IT Ischemia

(renal; preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
(pro)drugs)

IT Shock (circulatory collapse)

(septic; preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
(pro)drugs)

IT Brain, disease

(stroke; preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
(pro)drugs)

IT Inflammation

Intestine, disease

(ulcerative colitis; preparation of isoquinolinones as selective **c**
-Jun N-terminal kinase
inhibitors and (pro)drugs)

IT 289898-51-7, **JNK1**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
(pro)drugs)

IT 583833-01-6P, 6-Bromo-1-oxo-4-phenyl-2-(piperidin-3-ylmethyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride
583833-02-7P, 6-Bromo-1-oxo-4-phenyl-2-(piperidin-4-ylmethyl)-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride
847762-86-1P, 2-[3-(6-Chloro-1-oxo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-2-yl)propyl]isoindoline-1,3-dione 847762-87-2P,
2-[4-(6-Chloro-1-oxo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-2-yl)butyl]isoindoline-1,3-dione 847762-88-3P, 2-(4-Aminobutyl)-6-chloro-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-1-one hydrochloride
847762-89-4P, N-[4-(6-Chloro-1-oxo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-2-yl)butyl]acetamide 847762-90-7P,
(6-Bromo-1-oxo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-2-yl)acetonitrile 847762-91-8P, [6-Bromo-3-(1-hydroxypropyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]acetonitrile 847762-92-9P,
2-(2-Aminoethyl)-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride 847762-93-0P,
2-(3-Aminopropyl)-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride 847762-94-1P,
6-Bromo-2-[3-(methylamino)propyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride 847762-95-2P,
2-(3-Amino-2,2-dimethylpropyl)-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride
847762-96-3P, 2-(4-Aminobutyl)-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride
847762-97-4P, 6-Bromo-2-[2-(methylamino)ethyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester hydrochloride

847762-98-5P, 2-[4-(Acetylamino)butyl]-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847762-99-6P, 6-Bromo-2-[3-[(cyclohexylcarbonyl)amino]propyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847763-00-2P, 2-[3-[[3-(Acetylamino)benzoyl]amino]propyl]-6-bromo-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847763-01-3P 847763-02-4P 847763-03-5P, 6-Bromo-2-[[1-(isoquinolin-3-ylcarbonyl)piperidin-4-yl]methyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847763-04-6P, 6-Bromo-2-[[1-[4-(methylamino)-4-oxobut-2-enoyl]piperidin-4-yl]methyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847763-05-7P, 6-Bromo-2-[[1-(2-cyclopentylacetyl)piperidin-4-yl]methyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester 847763-06-8P 847763-07-9P 847763-08-0P 847763-09-1P 847763-10-4P 847763-11-5P 847763-12-6P 847763-13-7P 847763-14-8P 847763-15-9P 847763-16-0P 847763-17-1P 847763-18-2P 847763-19-3P 847763-20-6P 847763-21-7P 847763-22-8P 847763-23-9P 847763-24-0P 847763-25-1P 847763-26-2P 847763-27-3P 847763-28-4P 847763-29-5P 847763-30-8P 847763-31-9P 847763-32-0P 847763-33-1P 847763-34-2P 847763-35-3P 847763-36-4P 847763-37-5P 847763-38-6P 847763-39-7P 847763-40-0P 847763-41-1P 847763-42-2P 847763-43-3P 847763-44-4P 847763-45-5P 847763-46-6P 847763-47-7P 847763-48-8P 847763-49-9P 847763-50-2P 847763-51-3P 847763-52-4P 847763-53-5P 847763-54-6P 847763-55-7P 847763-56-8P 847763-57-9P 847763-58-0P 847763-59-1P 847763-60-4P 847763-61-5P 847763-62-6P 847763-63-7P 847763-64-8P 847763-65-9P 847763-66-0P 847763-67-1P 847763-68-2P 847763-69-3P 847763-70-6P 847763-71-7P 847763-72-8P 847763-73-9P 847763-74-0P 847763-75-1P 847763-76-2P 847763-77-3P 847763-79-5P 847763-81-9P 847763-83-1P 847763-85-3P 847763-87-5P 847763-89-7P 847763-91-1P 847763-93-3P 847763-95-5P 847763-97-7P 847763-99-9P 847764-01-6P 847764-03-8P 847764-04-9P 847764-05-0P 847764-06-1P 847764-07-2P 847764-08-3P 847764-09-4P 847764-10-7P 847764-11-8P 847764-12-9P 847764-13-0P 847764-14-1P 847764-15-2P 847764-16-3P 847764-17-4P 847764-18-5P 847764-19-6P 847764-20-9P 847764-21-0P 847764-22-1P 847764-23-2P 847764-24-3P 847764-25-4P 847764-26-5P 847764-27-6P 847764-28-7P 847764-29-8P 847764-30-1P 847764-31-2P 847764-32-3P 847764-33-4P 847764-34-5P 847764-35-6P 847764-36-7P 847764-37-8P 847764-38-9P 847764-39-0P 847764-40-3P 847764-41-4P 847764-42-5P 847764-43-6P 847764-44-7P 847764-45-8P 847764-46-9P 847764-47-0P 847764-48-1P 847764-49-2P 847764-50-5P 847764-51-6P 847764-52-7P 847764-53-8P 847764-54-9P 847764-55-0P 847764-56-1P 847764-57-2P 847764-58-3P 847764-59-4P 847764-60-7P 847764-61-8P 847764-62-9P 847764-63-0P 847764-64-1P 847764-65-2P 847764-66-3P 847764-67-4P 847764-68-5P 847764-69-6P 847764-70-9P 847764-71-0P 847764-72-1P 847764-73-2P 847764-74-3P 847764-75-4P 847764-76-5P 847764-77-6P 847764-78-7P 847764-79-8P 847764-80-1P 847764-81-2P 847764-82-3P 847764-83-4P 847764-84-5P 847764-85-6P 847764-86-7P 847764-87-8P 847764-88-9P 847764-89-0P 847764-90-3P 847764-91-4P 847764-92-5P 847764-93-6P 847764-94-7P 847764-95-8P 847764-96-9P 847764-97-0P 847764-98-1P 847764-99-2P 847765-00-8P 847765-01-9P 847765-02-0P 847765-03-1P 847765-04-2P 847765-05-3P 847765-06-4P 847765-07-5P 847765-08-6P 847765-09-7P 847765-10-0P 847765-11-1P 847765-12-2P 847765-13-3P 847765-14-4P 847765-15-5P 847765-16-6P 847765-17-7P 847765-18-8P 847765-19-9P 847765-20-2P 847765-21-3P 847765-22-4P 847765-23-5P 847765-24-6P 847765-25-7P 847765-26-8P 847765-27-9P 847765-28-0P 847765-29-1P 847765-30-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of isoquinolinones as selective c-Jun

**N-terminal kinase inhibitors and
(pro)drugs)**

IT	847765-31-5P	847765-32-6P	847765-33-7P	847765-34-8P	847765-35-9P
	847765-36-0P	847765-37-1P	847765-38-2P	847765-39-3P	847765-40-6P
	847765-41-7P	847765-42-8P	847765-43-9P	847765-44-0P	847765-45-1P
	847765-46-2P	847765-47-3P	847765-48-4P	847765-49-5P	847765-50-8P
	847765-51-9P	847765-52-0P	847765-53-1P	847765-54-2P	847765-55-3P
	847765-56-4P	847765-57-5P	847765-58-6P	847765-59-7P	847765-60-0P
	847765-61-1P	847765-62-2P	847765-63-3P	847765-64-4P	847765-65-5P
	847765-66-6P	847765-67-7P	847765-68-8P	847765-69-9P	847765-70-2P
	847765-71-3P	847765-72-4P	847765-73-5P	847765-74-6P	847765-75-7P
	847765-76-8P	847765-77-9P	847765-78-0P	847765-79-1P	847765-80-4P
	847765-81-5P	847765-82-6P	847765-83-7P	847765-84-8P	847765-85-9P
	847765-86-0P	847765-87-1P	847765-88-2P	847765-89-3P	847765-90-6P
	847765-92-8P	847765-93-9P	847765-94-0P	847765-95-1P	847765-96-2P
	847765-97-3P	847765-98-4P	847765-99-5P	847766-00-1P	847766-01-2P
	847766-02-3P	847766-03-4P	847766-04-5P	847766-05-6P	847766-06-7P
	847766-07-8P	847766-08-9P	847766-09-0P	847766-10-3P	847766-11-4P
	847766-12-5P	847766-13-6P	847766-14-7P	847766-15-8P	847766-16-9P
	847766-17-0P	847766-18-1P	847766-19-2P	847766-20-5P	847766-21-6P
	847766-22-7P	847766-23-8P	847766-24-9P	847766-25-0P	847766-26-1P
	847766-27-2P	847766-28-3P	847766-29-4P	847766-30-7P	847766-31-8P
	847766-32-9P	847766-33-0P	847766-34-1P	847766-35-2P	847766-36-3P
	847766-37-4P	847766-38-5P	847766-39-6P	847766-40-9P	847766-41-0P
	847766-42-1P	847766-43-2P	847766-44-3P	847766-45-4P	847766-46-5P
	847766-47-6P	847766-48-7P	847766-49-8P	847766-50-1P	847766-51-2P
	847766-52-3P	847766-53-4P	847766-54-5P, 2-[6-Bromo-3-(methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]propanoic acid	847766-55-6P,	
			2-[3-(Methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]propanoic acid	847766-56-7P, 2-[6-Bromo-3-(methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]-4-methylpentanoic acid	847766-57-8P,
			2-[3-(Methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]-4-methylpentanoic acid	847766-58-9P, [6-Bromo-3-(methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]acetic acid	847766-59-0P,
			[3-(Methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]acetic acid	847766-60-3P, 3-[6-Bromo-3-(methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]propanoic acid	847766-61-4P,
			3-[3-(Methoxycarbonyl)-1-oxo-4-phenyl-1,2-dihydroisoquinolin-2-yl]propanoic acid	847766-62-5P, 6-Bromo-2-[2-(cyclopropylamino)-1-methyl-2-oxoethyl]-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid	
	methyl ester	847766-63-6P	847766-64-7P	847766-65-8P	847766-66-9P
	847766-67-0P	847766-68-1P	847766-69-2P	847766-70-5P	847766-71-6P
	847766-72-7P	847766-73-8P	847766-74-9P	847766-75-0P	847766-76-1P
	847766-77-2P	847766-78-3P	847766-79-4P	847766-80-7P	847766-81-8P
	847766-82-9P	847766-83-0P	847766-84-1P	847766-85-2P	847766-86-3P
	847766-87-4P	847766-88-5P	847766-89-6P	847766-90-9P	847766-91-0P
	847766-92-1P	847766-93-2P	847766-94-3P	847766-95-4P	847766-96-5P
	847766-97-6P	847766-98-7P	847766-99-8P	847767-00-4P	847767-01-5P
	847767-02-6P	847767-03-7P	847767-04-8P	847767-05-9P	847767-06-0P
	847767-07-1P	847767-08-2P	847767-09-3P	847767-10-6P	847767-11-7P
	847767-12-8P	847767-13-9P	847767-14-0P	847767-15-1P	847767-16-2P
	847767-18-4P	847767-19-5P	847767-20-8P	847767-21-9P	847767-22-0P
	847767-23-1P	847767-24-2P	847767-25-3P	847767-26-4P	847767-27-5P
	847767-28-6P	847767-29-7P	847767-30-0P	847767-31-1P	847767-32-2P
	847767-33-3P	847767-34-4P	847767-35-5P	847767-36-6P	847767-37-7P
	847767-38-8P	847767-39-9P	847767-40-2P	847767-41-3P	847767-42-4P
	847767-43-5P	847767-44-6P	847767-45-7P	847767-46-8P	847767-47-9P
	847767-48-0P	847767-49-1P	847767-50-4P	847767-51-5P	847767-52-6P
	847767-53-7P	847767-54-8P	847767-55-9P	847767-56-0P	847767-57-1P
	847767-58-2P	847767-59-3P	847767-60-6P	847767-61-7P	847767-62-8P

847767-63-9P 847767-64-0P 847767-65-1P 847767-66-2P
 RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of isoquinolinones as selective c-Jun
 N-terminal kinase inhibitors and
 (pro)drugs)

IT	847767-67-3P	847767-68-4P	847767-69-5P	847767-70-8P	847767-71-9P
	847767-72-0P	847767-73-1P	847767-74-2P	847767-75-3P	847767-76-4P
	847767-77-5P	847767-78-6P	847767-79-7P	847767-80-0P	847767-81-1P
	847767-82-2P	847767-83-3P	847767-84-4P	847767-85-5P	847767-86-6P
	847767-87-7P	847767-88-8P	847767-89-9P	847767-90-2P	847767-91-3P
	847767-92-4P	847767-93-5P	847767-94-6P	847767-95-7P	847767-96-8P
	847767-97-9P	847767-98-0P	847767-99-1P	847768-00-7P	847768-01-8P
	847768-02-9P	847768-03-0P	847768-04-1P	847768-05-2P	847768-06-3P
	847768-07-4P	847768-08-5P	847768-09-6P	847768-10-9P	847768-11-0P
	847768-12-1P	847768-13-2P	847768-14-3P	847768-15-4P	847768-16-5P
	847768-17-6P	847768-18-7P	847768-19-8P	847768-20-1P	847768-21-2P
	847768-22-3P	847768-23-4P	847768-24-5P	847768-25-6P	847768-26-7P
	847768-27-8P	847768-28-9P	847768-29-0P	847768-30-3P	847768-31-4P
	847768-32-5P	847768-33-6P	847768-34-7P	847768-35-8P	847768-36-9P
	847768-37-0P	847768-38-1P	847768-39-2P	847768-41-6P	847768-42-7P
	847768-43-8P	847768-44-9P	847768-45-0P	847768-46-1P	847768-47-2P
	847768-48-3P	847768-49-4P	847768-50-7P	847768-51-8P	847768-52-9P
	847768-53-0P	847768-54-1P	847768-55-2P	847768-56-3P	847768-57-4P
	847768-58-5P	847768-59-6P	847768-60-9P	847768-61-0P	847768-62-1P
	847768-63-2P	847768-64-3P	847768-65-4P	847768-66-5P	847768-67-6P
	847768-68-7P	847768-69-8P	847768-70-1P	847768-71-2P	847768-72-3P
	847768-73-4P	847768-74-5P	847768-75-6P	847768-76-7P	847768-77-8P
	847768-78-9P	847768-79-0P	847768-80-3P	847768-81-4P	847768-82-5P
	847768-83-6P	847768-84-7P	847768-85-8P	847768-86-9P	847768-87-0P
	847768-88-1P				

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of isoquinolinones as selective c-Jun
 N-terminal kinase inhibitors and
 (pro)drugs)

IT	85-52-9, 2-Benzoylbenzoic acid	98-89-5, Cyclohexanecarboxylic acid
	302-01-2, Hydrazine, reactions	587-48-4, 3-(Acetylamino)benzoic acid
	590-17-0, Bromoacetonitrile	765-30-0, Cyclopropylamine
	5394-18-3, 2-(4-Bromobutyl)isoindoline-1,3-dione	1123-00-8,
	5460-29-7, 2-(3-Bromopropyl)isoindoline-1,3-dione	6624-49-3,
	3-Isoquinolinecarboxylic acid	13552-21-1, 1-Aminobutan-2-ol
	27532-96-3, Glycine tert-butyl ester hydrochloride	33184-56-4,
	2-Benzoyl-4-chlorobenzoic acid	53293-00-8, 5-Hexynoic acid
	144222-22-0, 4-Aminomethylpiperidine-1-carboxylic acid tert-butyl ester	133274-04-1
	412299-83-3, 2-Benzoyl-4-bromobenzoic acid	583837-71-2,
	6-Bromo-4-phenyl-3-isocoumarincarboxylic acid methyl ester	585571-02-4,
	1-Oxo-4-phenyl-1H-isochromene-3-carboxylic acid methyl ester	
	846022-53-5, 4-(Methylamino)-4-oxobut-2-enoic acid	

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of isoquinolinones as selective c-Jun
 N-terminal kinase inhibitors and
 (pro)drugs)

IT	583832-99-9P, 6-Bromo-2-(1-(tert-butoxycarbonyl)piperidin-4-ylmethyl)-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester
	844872-41-9P, 6-Bromo-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-1-one
	844872-46-4P, 6-Chloro-4-phenyl-3-propionyl-1,2-dihydroisoquinolin-1-one
	847768-89-2P 847768-90-5P, 6-Bromo-2-(2-tert-butoxy-1-methyl-2-oxoethyl)-

1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carboxylic acid methyl ester
 847768-91-6P, 2-(2-tert-Butoxy-1-methyl-2-oxoethyl)-1-oxo-4-phenyl-1,2-
 dihydroisoquinoline-3-carboxylic acid methyl ester 847768-92-7P,
 6-Bromo-2-(2-tert-butoxy-2-oxoethyl)-3-hydroxy-1-oxo-4-phenyl-1,2,3,4-
 tetrahydroisoquinoline-3-carboxylic acid methyl ester 847768-93-8P,
 6-Bromo-2-(2-tert-butoxy-2-oxoethyl)-1-oxo-4-phenyl-1,2-
 dihydroisoquinoline-3-carboxylic acid methyl ester 847768-94-9P,
 2-(2-tert-Butoxy-2-oxoethyl)-3-hydroxy-1-oxo-4-phenyl-1,2,3,4-
 tetrahydroisoquinoline-3-carboxylic acid methyl ester 847768-95-0P,
 2-(2-tert-Butoxy-2-oxoethyl)-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-
 carboxylic acid methyl ester

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
 (pro)drugs)

IT 847891-82-1 847891-83-2 847891-84-3 847891-85-4 847891-86-5
 847891-87-6 847891-88-7 847891-89-8

RL: PRP (Properties)

(unclaimed nucleotide sequence; preparation of isoquinolinones and their use
 as selective **c-Jun N-terminal**
kinase (JNK) inhibitors and (pro)drugs)

IT 289898-51-7, JNK1

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (preparation of isoquinolinones as selective **c-Jun**
N-terminal kinase inhibitors and
 (pro)drugs)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L640 ANSWER 19 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:212382 HCAPLUS

DOCUMENT NUMBER: 142:298010

TITLE: Preparation of isoquinolinone derivatives as JNK
 inhibitors, prodrugs thereof, and pharmaceuticals
 containing them

INVENTOR(S): Asano, Yasuomi; Fukumoto, Masashi; Ikata, Hideki

PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 67 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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JP 2005060246	A2	20050310	JP 2003-207416	20030812
PRIORITY APPLN. INFO.:			JP 2003-207416	20030812
OTHER SOURCE(S):	MARPAT 142:298010			

ED Entered STN: 10 Mar 2005

AB The derivs. I [benzene rings A and B may be substituted; X
 =(un)substituted chain hydrocarbylene; R1 = C6H4YZ-3 [benzene ring may be
 substituted; Y = direct bond, chain hydrocarbylene; Z = cyano,
 (un)substituted heterocyclyl, (un)substituted OH, (un)substituted thiol,
 substituted sulfinyl, (un)substituted sulfonyl, acyl, (un)substituted
 amino, (un)substituted carbamoyl, (un)esterified carboxyl], C6H4Y1Z1-4

(benzene ring may be substituted; Y1 = chain hydrocarbylene; Z1 = any group given for Z)] or their salts (14 exceptions are shown) and prodrugs of I are claimed. Also claimed are pharmaceuticals containing I or their salts or the prodrugs for prevention or treatment of JNK-related diseases, cardiac failure, cardiomyopathy, arteriosclerosis, rheumatoid arthritis, Crohn's disease, diabetes, Alzheimer's disease, parkinsonism, psoriasis, cancer, etc. Thus, (2E)-3-[4-[[6-chloro-1-oxo-4-phenyl-3-propionyl-2(1H)-isoquinolinyl]methyl]phenyl]acrylic acid (preparation given) at 10 μ M showed >95% inhibition against recombinant human JNK1. Pharmaceutical preps. containing I are also formulated.

IC ICM C07D217-24
ICS A61K031-472; A61P001-04; A61P001-16; A61P001-18; A61P003-04;
A61P003-10; A61P007-00; A61P009-00; A61P009-04; A61P009-10;
A61P009-12; A61P011-00; A61P011-06; A61P013-12; A61P017-00;
A61P017-02; A61P017-06; A61P019-02; A61P019-06
CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63
IT **Eye, disease**
(diabetic retinopathy; preparation of
phenylisoquinolinone derivs. as JNK inhibitors and their pharmaceutical
uses)
IT 155215-87-5, JNK 289898-51-7, JNK1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of phenylisoquinolinone derivs. as JNK inhibitors and their
pharmaceutical uses)
IT 289898-51-7, JNK1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of phenylisoquinolinone derivs. as JNK inhibitors and their
pharmaceutical uses)
RN 289898-51-7 HCAPLUS
CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L640 ANSWER 20 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:180587 HCAPLUS

DOCUMENT NUMBER: 142:371191

TITLE: Expression of MUK/DLK/ZPK, an activator of the JNK
pathway, in the nervous systems of the developing
mouse embryo

AUTHOR(S): Hirai, Syu-ichi; Kawaguchi, Atumi; Suenaga, Jun; Ono,
Makiko; Cui, De Feng; Ohno, Shigeo

CORPORATE SOURCE: Department of Molecular Biology, Yokohama City
University Graduate School of Medical Science, 3-9,
Fukuura, Kanazawa-ku, Yokohama, 236-0004, Japan

SOURCE: Gene Expression Patterns (2005), 5(4), 517-523

CODEN: GEPEAD; ISSN: 1567-133X

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 04 Mar 2005

AB **C-Jun N-terminal kinase**

(JNK) is implicated in regulating the various cellular events during
neural development that include differentiation, apoptosis and migration.
MUK/DLK/ZPK is a MAP kinase kinase kinase (MAPKKK) enzyme that activates
JNK via MAP kinase kinases (MAPKK) such as MKK7. We show here that the
expression of MUK/DLK/ZPK protein in the developing mouse embryo is almost
totally specific for the neural tissues, including central, peripheral,
and autonomic nervous systems. The only obvious exception is the liver,

in which the protein is temporally expressed at around E11. The expression becomes obvious in the neurons of the brain and neural crest tissues at embryonic day 10 (E10) after neuron production is initiated. By E14, MUK/DLK/ZPK proteins are found in various neural tissues including the brain, spinal cord, sensory ganglia (such as trigeminal and dorsal root ganglia), and the sympathetic and visceral nerves. The localization of MUK/DLK/ZPK protein in neural cells almost consistently overlapped that of β III-tubulin, a neuron specific tubulin isoform, and both proteins were more concentrated in axons than in cell bodies and dendrites. The intensely overlapping localization of β III-tubulin and MUK/DLK/ZPK indicated that this protein kinase is tightly associated with the microtubules of neurons.

CC 13-3 (Mammalian Biochemistry)

IT **Eye**

(retina, neural; expression of activator of JNK pathway MUK/DLK/ZPK in nervous systems of developing mouse embryo)

IT 155215-87-5, **C-Jun N-terminal**

kinase 179241-70-4, Protein kinase MUK

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(expression of activator of JNK pathway MUK/DLK/ZPK in nervous systems of developing mouse embryo)

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 21 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:367279 HCAPLUS

DOCUMENT NUMBER: 142:408242

TITLE: MAPKs mediate the activation of cytosolic phospholipase A2 by amyloid β (25-35) peptide in bovine retina pericytes

AUTHOR(S): Nicotra, Ambra; Lupo, Gabriella; Giurdanella, Giovanni; Anfusio, Carmelina D.; Ragusa, Nicolo; Tirolo, Cataldo; Marchetti, Bianca; Alberghina, Mario
CORPORATE SOURCE: Department of Biochemistry, University of Catania, Catania, 95125, Italy

SOURCE: Biochimica et Biophysica Acta, Molecular and Cell Biology of Lipids (2005), 1733(2-3), 172-186
CODEN: BBMLFG; ISSN: 1388-1981

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 29 Apr 2005

AB We have previously shown that, in bovine retina pericytes, amyloid β (1-42) and its truncated form containing amino acids 25-35, after 24 h treatment, stimulate arachidonic acid (AA) release and phosphatidylcholine hydrolysis, by activation of both cytosolic (cPLA2) and Ca^{2+} -independent (iPLA2) phospholipase A2. A putative role for MAP kinases in this process emerged. Here the authors studied the role of the MAP-kinase family as well as both cPLA2 and iPLA2 mRNA expression by a semi-quant. reverse transcriptase-polymerase chain reaction (RT-PCR) in the same sublethal model of amyloid- β (A β) damage to pericytes in vitro. G3A β (25-35) peptide evoked AA release as well as stimulated phosphorylation of ERK1/2, p38 MAPKs and cPLA2, but not c-Jun N-terminal kinase (JNK/SAPK). PD98059, an inhibitor of ERK-activating kinase MEK-1, and SB203580, an inhibitor of p38 protein kinase, abolished the stimulation of AA release and MAPK activities. In cells stimulated by A β (25-35) peptide, Western blotting and confocal microscopy analyses confirmed either an increase in the phosphorylated form of ERKs and p38 or their nuclear translocation. A complete inhibition of MAPK activation and AA release

was also observed when pericytes were treated with GF109203X, a general PKC inhibitor, indicating the important role of both PKC and the 2 MAPKs in mediating the A β peptide response. Compared with samples untreated or treated with reverse A β (35-25) peptide, pretreatment with 50 μ M A β (25-35) for 24 h significantly increased the level of constitutively expressed iPLA2 mRNA by 25%, which seems to depend on the activation of kinases. By contrast, the level of cPLA2 mRNA remained unchanged. Together, these data link either the stimulation of PKC-ERK-p38 cascades or PLA2 activity by A β peptide to prooxidant mechanism induced by amyloid, which may initially stimulate the cell reaction as well as metabolic repair, such as during inflammation.

CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 14

IT Eye
(retina; PKC and MAPK-mediated activation of cytosolic phospholipase A2 and arachidonic acid release by amyloid β (25-35) in bovine retina pericytes)

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 22 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1059119 HCAPLUS

DOCUMENT NUMBER: 142:32932

TITLE: Combination therapy for cancer and other proliferative disorders

INVENTOR(S): Blatt, Lawrence M.; Seiwert, Scott D.; Ozes, Osman N.

PATENT ASSIGNEE(S): Intermune, Inc., USA

SOURCE: PCT Int. Appl., 635 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004105684	A2	20041209	WO 2004-US15346	20040513
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.:
 US 2003-471841P P 20030516
 US 2003-485474P P 20030708
 US 2003-511259P P 20031014
 US 2003-511280P P 20031014
 US 2003-511415P P 20031014
 US 2003-514173P P 20031024
 US 2004-561940P P 20040413

ED Entered STN: 10 Dec 2004

AB The invention provides methods of treating proliferative disorders, including angiogenesis-mediated disorders, cancer, and fibrotic disorders. In some embodiments, the methods involve administering a Type II interferon receptor agonist and a Type I interferon receptor agonist. In

other embodiments, the methods involve administering a Type II interferon receptor agonist, a stress-activated protein kinase (SAPK) inhibitor, and a third therapeutic agent. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a vascular endothelial growth factor (VEGF) antagonist. In other embodiments, the methods involve administering a VEGF antagonist and a SAPK inhibitor. The invention further provides methods of treating fibrotic disorders. In some embodiments, the methods involve administering a Type I interferon receptor agonist, a Type II interferon receptor agonist; and a tumor necrosis factor (TNF) antagonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a TNF antagonist. In other embodiments, the methods involve administering pirfenidone or a pirfenidone analog and a TNF antagonist. In other embodiments, the methods involve administering a Type II interferon receptor agonist and a transforming growth factor- β (TGF- β) antagonist. In other embodiments, the methods involve administering a SAPK inhibitor alone or in combination with a Type II interferon receptor agonist. In other embodiments, the methods involve administering N-acetylcysteine (NAC) and a SAPK inhibitor. In other embodiments, the methods involve administering NAC and a Type II interferon receptor agonist.

IC ICM A61K

CC 1-6 (Pharmacology)

IT **Eye**

(cornea, transplant; combination therapy for cancer and other proliferative disorders)

IT Transplant and Transplantation

(cornea; combination therapy for cancer and other proliferative disorders)

IT **Eye, disease**

(diabetic retinopathy; combination therapy for cancer and other proliferative disorders)

IT **Eye, disease**

(macula, senile degeneration; combination therapy for cancer and other proliferative disorders)

IT **Glaucoma (disease)**

(neovascular; combination therapy for cancer and other proliferative disorders)

IT **Eye, disease**

(retinopathy; combination therapy for cancer and other proliferative disorders)

IT **Eye, disease**

(retrolental fibroplasia; combination therapy for cancer and other proliferative disorders)

IT 90698-26-3, P70S6 Kinase 101463-26-7, Platelet-derived growth factor receptor kinase 103843-29-4, Insulin-like growth factor-1 receptor kinase 114051-78-4, Lck kinase 136396-12-8, Platelet-derived growth factor receptor β kinase 137632-06-5, Csk protein kinase 138674-26-7, Syk kinase 139691-76-2, c-Raf kinase 140208-17-9, Lyn kinase 140208-24-8, Timp-1 141349-86-2, Cdk2 kinase 141349-87-3, Fyn kinase 141349-91-9, Yes kinase 141460-90-4, Fes kinase 142008-29-5, Protein kinase A 142243-02-5, MAPK 142805-58-1, MEK1 kinase 143375-65-9, Cdk1 kinase 144697-17-6, c-Src kinase 146838-30-4, MAPKAP-K2 kinase 147014-96-8, Cdk5 kinase 147230-71-5, Gene FLT3 receptor kinase 148047-34-1, Zap-70 kinase 149146-03-2, FGFR3 tyrosine kinase 149146-91-8, TrkB protein tyrosine kinase 153190-63-7, Axl receptor tyrosine kinase 153190-71-7, Cdk3 kinase 154907-65-0, CHK1 kinase 161384-20-9, Protein kinase C μ 165245-96-5, Stress-activated protein kinase p38 α 176023-64-6, p38 γ Map kinase 178037-70-2, Protein kinase SGK 178303-46-3, Bmx tyrosine kinase 179800-23-8, Stress-activated protein kinase-2b 182938-08-5, Protein

kinase ROCK II 185156-08-5, Protein kinase PRK2 191808-15-8, Pdk1
 kinase 192140-83-3, PAK2 kinase 192333-55-4, Sapk4 kinase
 212378-03-5, Protein kinase PRAK 244634-79-5, CHK2 protein kinase
 289898-51-7, Jnk1 kinase 289899-93-0, Jnk2
 kinase 291756-39-3, Jnk3 kinase 330197-29-0, Cdk7 kinase
 333425-95-9, Protein kinase D2 362516-16-3, IKK α kinase
 362517-43-9, IKK β kinase 366806-33-9, Protein kinase CK2
 377752-08-4, Rsk2 protein kinase 389133-24-8, Rsk3 protein kinase
 443900-95-6, Glycogen synthase kinase 3 β 458560-40-2, Aurora-A
 kinase 476196-08-4, Protein kinase CaMKIV 488850-98-2, Protein kinase
 C η 553648-93-4, Glycogen synthase kinase 3 α

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (combination therapy for cancer and other proliferative disorders)

IT 289898-51-7, Jnk1 kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (combination therapy for cancer and other proliferative disorders)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L640 ANSWER 23 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:995980 HCAPLUS

DOCUMENT NUMBER: 141:424112

TITLE: Preparation and use of pyridinyl acetoneitriles as
 protein kinase modulators, in particular GSK3 and JNK
 inhibitors, for treating especially an autoimmune,
 neurodegenerative, and neuronal disorder

INVENTOR(S): Schwarz, Matthias; Gaillard, Pascale; Gotteland,
 Jean-Pierre; Thomas, Russell J.; Page, Patrick

PATENT ASSIGNEE(S): Applied Research Systems Ars Holding N. V., Neth.
 Antilles

SOURCE: PCT Int. Appl., 118 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004098607	A1	20041118	WO 2004-EP4808	20040503
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.: EP 2003-101281 A 20030508

OTHER SOURCE(S): MARPAT 141:424112

ED Entered STN: 19 Nov 2004

AB The invention is related to the use of pyridinyl acetoneitriles X-CH(CN)-G
 [I, wherein X = (un)substituted pyridinyl group; G = (un)substituted
 pyridinyl, pyrimidinyl, triazinyl] as well as their tautomers, geometrical

isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts as modulators of the protein kinase signalling pathways, particularly the one involving Glycogen Synthase Kinase 3 (GSK3) or **c-Jun N-terminal kinase** (JNK). The invention is also related to the preparation of pyridinyl acetonitriles. For example, II was prepared in 2 steps by reacting 2-pyridineacetonitrile with 2,4-dichloro-5-methylpyrimidine in THF, followed by aminolysis of chloride with cyclopentylamine. Selected I displayed IC₅₀ < 1 μ M for the inhibition of JNK3 and GSK3 β kinase in in vitro biol. assays. I and their pharmaceutical compns. are useful for treating neurodegenerative, neuronal, inflammatory, and cardiovascular diseases, and metabolic disorders.

IC ICM A61K031-505
ICS A61K031-53; A61P037-02; A61P025-16; C07D401-06
CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63
IT Alzheimer's disease
Anti-Alzheimer's agents
Anti-inflammatory agents
Anti-ischemic agents
Antiartherosclerotics
Antiarthritics
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antiglaucoma agents
Antiobesity agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Arteriosclerosis
Arthritis
Asthma
Autoimmune disease
Cardiovascular agents
Cardiovascular system, disease
Diabetes mellitus
Epilepsy
Glaucoma (disease)
Human
Immunomodulators
Inflammation
Ischemia
Kidney, neoplasm
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Multiple sclerosis
Neoplasm
Nerve, disease
Nervous system agents
Obesity
Ovary, neoplasm
Pancreas, neoplasm
Parkinson's disease
Prostate gland, neoplasm
Rheumatoid arthritis
Testis, neoplasm
Transplant rejection
(preparation and use of pyridinyl acetonitriles as GSK3 and JNK inhibitors)

for treating especially an autoimmune, neurodegenerative, and neuronal disorder)

IT **Eye, disease**

(retinopathy; preparation and use of pyridinyl acetonitriles as GSK3 and JNK inhibitors for treating especially an autoimmune, neurodegenerative, and neuronal disorder)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 24 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:399888 HCAPLUS

DOCUMENT NUMBER: 141:85946

TITLE: Regulation of the Circadian Oscillator in *Xenopus* Retinal Photoreceptors by Protein Kinases Sensitive to the Stress-activated Protein Kinase Inhibitor, SB 203580

AUTHOR(S): Hasegawa, Minoru; Cahill, Gregory M.

CORPORATE SOURCE: Department of Biology and Biochemistry, University of Houston, Houston, TX, 77204-5001, USA

SOURCE: Journal of Biological Chemistry (2004), 279(21), 22738-22746

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 17 May 2004

AB Circadian rhythms are generated by transcriptional and translational feedback loops. Stress-activated protein kinases (SAPKs) are known to regulate transcription factors in response to a variety of extracellular stimuli. In the present study, the authors examined whether the SAPKs play a role in the circadian system in cultured *Xenopus* retinal photoreceptor layers. A 6-h pulse of SB 203580, an inhibitor of SAPKs, reset the circadian rhythm of melatonin in a phase-dependent manner similar to dark pulses. This phase-shifting effect was dose-dependent over the range of 1-100 μ M. Treatment with SB 203580 also affected light-induced phase shifts, and light had no effect on the circadian oscillator in the presence of 100 μ M SB 203580. In-gel kinase assays showed that SB 203580 selectively inhibited a small group of protein kinases in the photoreceptor cells. These SB 203580-sensitive kinases correspond to two isoforms of phosphorylated p38 MAPK and three isoforms of c-Jun N-terminal kinase (JNK).

Further in vitro study demonstrated that SB 203580 also inhibited casein kinase I ϵ (CKI ϵ), which has been shown to regulate circadian rhythms in several organisms. However, a pharmacol. inhibition of CKI reset the circadian oscillator in a phase-dependent manner distinct from that of SB 203580. This argues against a primary role of CKI in the phase-shifting effects of SB 203580. These results suggest that SB 203580 affects the circadian system by inhibiting p38 MAPKs or JNKs and that these protein kinases are candidate cellular signals in the regulation of the circadian oscillator in the *Xenopus* retinal photoreceptors.

CC 12-6 (Nonmammalian Biochemistry)

IT **Eye**

(photoreceptor; p38 MAPKs and JNKs protein kinases are candidate cellular signals in the regulation of the circadian oscillator in *Xenopus* retinal photoreceptors)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 25 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:149349 HCAPLUS
DOCUMENT NUMBER: 140:337166
TITLE: Influence of interleukin-1 beta induction and
mitogen-activated protein kinase phosphorylation on
optic nerve ligation-induced matrix
metalloproteinase-9 activation in the retina
AUTHOR(S): Zhang, Xu; Chintala, Shravan K.
CORPORATE SOURCE: Eye Research Institute, Oakland University, Rochester,
MI, 48309, USA
SOURCE: Experimental Eye Research (2004), 78(4), 849-860
CODEN: EXERA6; ISSN: 0014-4835
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

ED Entered STN: 24 Feb 2004

AB Ischemic damage to the retina is a multifaceted process that results in irreversible loss of ganglion cells and blinding disease. Although the mechanisms underlying ischemia-induced ganglion cell death in the retina are not clearly understood, we have recently reported that retinal damage induced by ligation of the optic nerve results in increased matrix metalloproteinase-9 (MMP-9) synthesis and promotes ganglion cell loss. In this study, we have investigated the roles of IL-1-beta and mitogen activated protein kinases in MMP-9 induction in the retina. Optic nerve ligation led to a transient increase in IL-1-beta and MMP-9 levels and phosphorylation of p42/p44 mitogen activated protein kinases (extracellular signal-regulated kinases, ERK1 and ERK2) in the retina. We found no significant increase in phosphorylation of p38 MAP kinase or c-jun N-terminal kinases indicating that ERK1/2 plays a major role in MMP-9 induction. Intravitreal injection of IL-1 receptor antagonist (IL-1Ra) or MAP kinase inhibitor U0126 significantly decreased both ERK1/2 phosphorylation and MMP-9 induction suggesting that interruption of this cascade might attenuate retinal damage. In support of this, intravitreal injection of IL-1Ra and U0126 offered significant protection against optic nerve-induced retinal damage. These results suggest that optic nerve ligation-induced IL-1-beta promotes retinal damage by increasing MMP-9 synthesis in the retina.

CC 14-10 (Mammalian Pathological Biochemistry)

IT Eye

(ganglion cell; influence of interleukin-1 beta induction and mitogen-activated protein kinase phosphorylation on optic nerve ligation-induced matrix metalloproteinase-9 activation in retina)

IT Eye

(retina; influence of interleukin-1 beta induction and mitogen-activated protein kinase phosphorylation on optic nerve ligation-induced matrix metalloproteinase-9 activation in retina)

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 26 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1048457 HCAPLUS
DOCUMENT NUMBER: 142:20549
TITLE: Synapsin and synaptic vesicle protein expression during embryonic and post-natal lens fiber cell differentiation
AUTHOR(S): Frederikse, Peter H.; Yun, Esther; Kao, Hung-Teh; Zigler, J. Samuel, Jr.; Sun, Qian; Qazi, A. Sami
CORPORATE SOURCE: Department of Pharmacology & Physiology, UMDNJ-New Jersey Medical School, Newark, NJ, USA
SOURCE: Molecular Vision (2004), 10, 794-804

CODEN: MVEPFB; ISSN: 1090-0535

URL: [http://www.molvis.org/molvis/v10/a94/frederikse.p](http://www.molvis.org/molvis/v10/a94/frederikse.pdf)
df

PUBLISHER:

Molecular Vision

DOCUMENT TYPE:

Journal; (online computer file)

LANGUAGE:

English

ED Entered STN: 08 Dec 2004

AB Reorganization of cytoskeleton and membrane biogenesis are dynamically coordinated during lens fiber cell differentiation and development to produce an organ with precise dimensions and optical properties. Cargo vesicle trafficking is fundamental to cell elongation and has also been implicated in degenerative disease mechanisms. Alzheimer precursor protein (A β PP) acts with kinesin, synapsin, and synaptic vesicle proteins to mediate cargo vesicle transport and membrane fusion in neurons. In our previous studies we demonstrated that A β PP is also a key element in lens fiber cell formation, and in early-onset cataract that occurs along with early-onset Alzheimer disease in Down syndrome. In the present study we examine lens expression and regulation of a complement of genes associated with cargo and synaptic vesicle transport in neurons. RT-PCR, immunoblot, and immunohistochem. methods were used to characterize expression of A β PP and kinesin associated-motor proteins, synapsins, and synaptic vesicle proteins in mouse and rat embryonic, post-natal, and adult lenses. Phospho-specific anti-synapsin antibodies were used to determine the distributions of site-1 phosphorylated and dephosphorylated synapsin protein. We demonstrate that a substantial complement of cargo and synaptic vesicle proteins involved in A β PP mediated vesicle transport are expressed in lenses along the anterior-posterior axis of fiber cells in embryonic and adult lenses, consistent with vesicles, actin filaments, and neuron-like arrangement of microtubules in lenses shown by others. We identify temporal regulation of synapsins I, II, and III during embryonic and post-natal lens development consistent with their roles in neurons. Regulation of vesicle cytoskeleton attachment, actin polymerization, and the capacity to stimulate cell differentiation by synapsins are governed in large part by phosphorylation at a conserved Ser9 residue (site-1). We demonstrate discrete distributions of Ser9 phospho- and dephospho-synapsins along the axial length of rapidly elongating embryonic lens fiber cells, and decreased levels of site-1 phosphorylated synapsins in adult lenses. The present findings demonstrate several fundamental parallels between lens and neuron vesicle trafficking cell biol. and development, and suggest that more extensive A β PP related vesicle trafficking disease mechanisms may be shared by lens and brain.

CC 13-3 (Mammalian Biochemistry)

IT Proteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(JIP-1 (c-Jun N-terminal

kinase-interacting protein-1), JIP-1b isoform; expression of synapsins, Alzheimer precursor protein-kinesin-associated proteins, and synaptic vesicle proteins during embryonic and post-natal lens fiber cell differentiation)

IT Eye

(lens, fiber; expression of synapsins, Alzheimer precursor protein-kinesin-associated proteins, and synaptic vesicle proteins during embryonic and post-natal lens fiber cell differentiation)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 27 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:640356 HCAPLUS

DOCUMENT NUMBER: 141:204131

TITLE: Impaired cytoskeletal organization and membrane

integrity in lens fibers of a Rho GTPase functional knockout transgenic mouse

AUTHOR(S): Maddala, Rupalatha; Deng, Pei-Feng; Costello, Joseph M.; Wawrousek, Eric F.; Zigler, Jacob S., Jr.; Rao, Vasantha P.

CORPORATE SOURCE: Department of Ophthalmology, Duke University Medical Center, Durham, NC, USA

SOURCE: Laboratory Investigation (2004), 84(6), 679-692
CODEN: LAINAW; ISSN: 0023-6837

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 09 Aug 2004

AB To investigate the effects of Rho GTPase inactivation on lens fiber cell cytoskeletal and morphol. integrity, a transgenic mouse model expressing C3-exoenzyme (a bacterial toxin) in a lens-specific manner was utilized. Cryosections of whole eyes from C3 transgenic mice and littermate controls were stained for F-actin with rhodamine-phalloidin or immunostained for β -catenin, aquaporin-0 or connexin-50, and confocal images were recorded. Lens fiber cell morphol. was examined at both light and electron microscopic levels. To investigate the influence of Rho GTPase inactivation on the profiles of gene expression, cDNA libraries generated from transgenic and littermate control mouse lenses were screened by cDNA microarray anal. In contrast to the wild-type lens, fiber cells of the transgenic lens were grossly swollen and disorganized, with abnormal membrane architecture. Staining of F-actin, β -catenin, aquaporin-0 and connexin-50 was reduced dramatically in the C3 transgenic lens as compared to controls. Western blot anal. and cDNA microarray anal. did not reveal any noticeable decreases in actin, β -catenin and aquaporin-0 protein levels or expression in C3 transgenic lenses, indicating that altered cytoskeletal organization in response to Rho GTPase inactivation might underlie the noted changes in staining for these proteins. Addnl., cDNA microarray anal. of C3 lens revealed altered expression (at least two-fold, compared to littermate controls) of 44 genes. These include genes encoding extracellular matrix and basement membrane proteins, cell survival and apoptotic pathways, and ion and protein transport. These data indicate that disruption of Rho GTPase function in the developing mouse lens results in abnormal cytoskeletal organization, fiber cell interactions, impaired lens fiber cell morphol. and altered gene expression of cellular proteins involved in diverse functions. This work reveals that the morphol. and cytoskeletal abnormalities triggered upon Rho GTPase inactivation in lens could be one of the important insults associated with cataract formation in C3 transgenic mouse lens.

CC 13-6 (Mammalian Biochemistry)

IT **Eye**
Transparency
(lens; effects of Rho GTPase on morphol., actin cytoskeletal organization, membrane integrity, adherens junction formation, and distribution of water channel and gap junction proteins in lens fibers)

IT 143550-91-8, Granzyme F **289898-51-7, JNK1 kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cDNA microarray of expression of genes encoding extracellular matrix and basement membrane proteins, apoptotic pathways, and ion and protein transport in Rho GTPase knockout mouse)

IT **289898-51-7, JNK1 kinase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cDNA microarray of expression of genes encoding extracellular matrix and basement membrane proteins, apoptotic pathways, and ion and protein

transport in Rho GTPase knockout mouse)

RN 289898-51-7 HCAPLUS

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 28 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:714017 HCAPLUS

DOCUMENT NUMBER: 141:421749

TITLE: Human α A- and α B-crystallins prevent

UVA-induced apoptosis through regulation of PKC α , RAF/MEK/ERK and AKT signaling pathways

AUTHOR(S): Liu, Jin-Ping; Schlosser, Ryan; Ma, Wei-Ya; Dong, Zigang; Feng, Hao; Liu, Long; Huang, Xiao-Qing; Liu, Yan; Li, David Wan-Cheng

CORPORATE SOURCE: The Hormel Institute, University of Minnesota, Austin, MN, 55912, USA

SOURCE: Experimental Eye Research (2004), 79(3), 393-403
CODEN: EXERA6; ISSN: 0014-4835

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 01 Sep 2004

AB α A- and α B-crystallins are distinct antiapoptotic regulators. Regarding the antiapoptotic mechanisms, we have previously demonstrated that under staurosporine treatment, H α A- and H α B-crystallins can interact with Bax and Bcl-XS, proapoptotic members of the Bcl-2 family, to sequester their translocation into mitochondria, and thus prevent the staurosporine-induced apoptosis. In the present study, we further compared the anti-apoptotic mechanisms of H α A- and H α B-crystallin in preventing human lens epithelial cells from UVA-induced apoptosis. UVA-irradiation of human lens epithelial cells turned on the apoptotic death program. Moreover, associated with the activation of the death program, UVA also activated the RAF/MEK/ERK signaling pathway. In contrast, p38 kinase and JNK1/2 signaling pathways were not activated. Inhibition of the RAF/MEK/ERK pathway by a dominant neg. mutant RAF1 greatly attenuated UVA-induced apoptosis. Expression of the exogenous human α B-crystallin prevented UVA-induced activation of RAF/MEK/ERK pathway and thus substantially abrogated UVA-induced apoptosis. In contrast, expression of the exogenous human α A-crystallin did not prevent UVA-induced activation of RAF/MEK/ERK pathway. Instead, it activated AKT kinase pathway to promote survival and thus counteracted the UVA-induced apoptosis. Together, our results for the first time reveal that by regulating multiple signaling pathways the two α -crystallins can prevent stress-induced apoptosis through different mechanisms.

CC 8-7 (Radiation Biochemistry)

ST UVA radiation eye lens crystallin apoptosis

IT Eye

(lens; anti-apoptotic mechanisms of H α A- and H α B-crystallin in preventing human lens epithelial cells from UVA-induced apoptosis)

IT 137632-07-6, ERK1 protein kinase 137632-08-7, ERK2 protein kinase

142805-58-1, MEK1 protein kinase 150316-14-6, MEK2 protein kinase

289898-51-7, JNK1 protein kinase

289899-93-0, JNK2 protein kinase

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anti-apoptotic mechanisms of H α A- and H α B-crystallin in

preventing human lens epithelial cells from UVA-induced apoptosis)
 IT 289898-51-7, **JNK1 protein kinase**
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (anti-apoptotic mechanisms of H α A- and H α B-crystallin in
 preventing human lens epithelial cells from UVA-induced apoptosis)
 RN 289898-51-7 HCAPLUS
 CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
 INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 29 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:1046586 HCAPLUS

DOCUMENT NUMBER: 142:73338

TITLE: NF- κ B activation prevents apoptotic oxidative
 stress via an increase of both thioredoxin and MnSOD
 levels in TNF α -treated Ewing sarcoma cells

AUTHOR(S): Djavaheri-Mergny, Mojgan; Javelaud, Delphine;
 Wietzerbin, Juana; Besancon, Francoise

CORPORATE SOURCE: Institut Curie, Section de recherche, INSERM U365,
 Paris, 75248, Fr.

SOURCE: FEBS Letters (2004), 578(1-2), 111-115

CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 07 Dec 2004

AB Repression of activation of **c-Jun N-terminal kinase** (JNK) participates in the anti-apoptotic
 effect of nuclear factor- κ B (NF- κ B) in TNF α -treated
 Ewing sarcoma cells. As oxidative stress is one of the most prominent
 activators of JNK, the authors investigated the relation between
 TNF α -induced NF- κ B activation and the control of oxidative
 stress. Inhibition of NF- κ B activation resulted in an increase in
 TNF α -induced ROS production, lipid peroxidn. and protein oxidation Those
 ROS and lipid peroxides were both involved in TNF α -induced
 apoptosis, whereas only ROS elevation triggered sustained JNK activation.
 TNF α increased the level of two antioxidant enzymes, thioredoxin and
 manganese superoxide dismutase by an NF- κ B-dependent mechanism.
 Inhibition of expression or activity of these enzymes sensitized cells to
 TNF α -induced apoptosis, indicating their functional role in
 protection from cell death. Thus, agents that inhibit activities of these
 enzymes may prove helpful in the treatment of Ewing tumors.

CC 15-10 (Immunochemistry)

Section cross-reference(s): 14

IT **Eye**

(rod outer segment; NF- κ B activation prevents apoptotic oxidative
 stress via an increase of both thioredoxin and MnSOD levels in
 TNF α -treated Ewing sarcoma cells)

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 30 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:478408 HCAPLUS

DOCUMENT NUMBER: 141:205442

TITLE: Expression of human β -defensin 2 mRNA by
 lipopolysaccharide in human **corneal**
 epithelial cells

AUTHOR(S) : Bae, Eon-Hee; Park, Keon-Wuk; Kim, Jong-Wook; Jang, Byeong-Churl; Lim, Ki-Jo; Jung, Tae-Young; Kwon, Young-Kyu; Shin, Sang-Woo; Kim, Sang-Pyo; Park, Jong-Hyun; Kwon, Taeg Kyu; Baek, Won-Ki; Suh, Min-Ho; Suh, Seong-Il

CORPORATE SOURCE: Hanbit Eye and laser center, Taegu, 700-070, S. Korea

SOURCE: Journal of Bacteriology and Virology (2004), 34(1), 27-38
CODEN: JBVOAH; ISSN: 1598-2467

PUBLISHER: Journal of Bacteriology and Virology

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 14 Jun 2004

AB Recently the transcriptional up-regulation of human β -defensin 2 (HBD-2) by lipopolysaccharide (LPS) was found to be associated with NF- κ B binding site. Although the general mechanisms of NF- κ B activation by LPS stimulation are well understood, less is known about the signal transduction pathway leading to LPS-induced NF- κ B activation in human corneal epithelial (HCE) cells. The aim of this study was to investigate the intracellular signals involved in LPS-induced HBD-2 mRNA expression in HCE cells. Pretreatments of inhibitors for NF- κ B, protein tyrosine kinase, p38 mitogen activated protein kinase (MAPK), and c-Jun N-terminal kinase (JNK) attenuated the LPS-induced NF- κ B DNA binding activity and HBD-2 mRNA expression. Furthermore, pretreatments with inhibitors for protein kinase C (PKC), phosphatidylcholine-phospholipase C, phosphatidylinositol-phospholipase C, or phosphatidate phosphohydrolase prevented LPS-induced HBD-2 mRNA expression and HBD-2 promoter-driven luciferase activity. However, the increased expression of HBD-2 mRNA and the increased DNA binding activity of NF- κ B induced by LPS were not changed by the blockage of extracellular signal-regulated kinase (ERK) and of addition of antioxidants. Forskolin, a protein kinase A (PKA) agonist did not induce HBD-2 mRNA expression. These data demonstrate that LPS-induced HBD-2 mRNA expression via NF- κ B is, at least in part, dependent on PKC, p38 MAPK, JNK, and protein tyrosine kinase status, but appears to be independent on PKA, ERK and ROS in HCE cells. Taken together, there may be more than one signaling pathway that leads to LPS-induced up-regulation of HBD-2 mRNA expression in HCE cells.

CC 15-7 (Immunocytochemistry)

ST lipopolysaccharide NF κ B signaling beta defensin transcription

IT corneal epithelium

IT Transcription factors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (NF- κ B (nuclear factor of κ light chain gene enhancer in B-cells); signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT Transcriptional regulation

(activation; signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT Lipopolysaccharides

RL: BSU (Biological study, unclassified); BIOL (Biological study) (bacterial; signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT Eye

(cornea, epithelium; signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT Epithelium
(corneal; signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT Human
Signal transduction, biological
(signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

IT 9025-77-8, Phosphatidate phosphohydrolase 63551-76-8, Phosphatidylinositol-phospholipase C 80449-02-1, Protein tyrosine kinase 102784-33-8, Phosphatidylcholine-phospholipase C 141436-78-4, Protein kinase C 155215-87-5, JNK kinase 165245-96-5, p38 MAP kinase 426206-97-5, β -Defensin 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(signaling pathways involved in transcriptional up-regulation of human β -defensin 2 by lipopolysaccharide in corneal epithelial cells)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 31 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:405556 HCAPLUS

DOCUMENT NUMBER: 139:96823

TITLE: JNK initiates a cytokine cascade that causes Pax2 expression and closure of the optic fissure

AUTHOR(S): Weston, Claire R.; Wong, Anthony; Hall, J. Perry; Goad, Mary E. P.; Flavell, Richard A.; Davis, Roger J.

CORPORATE SOURCE: Howard Hughes Medical Institute and Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA, 01605, USA

SOURCE: Genes & Development (2003), 17(10), 1271-1280

CODEN: GEDEEP; ISSN: 0890-9369

PUBLISHER: Cold Spring Harbor Laboratory Press

DOCUMENT TYPE: Journal

LANGUAGE: English

ED Entered STN: 28 May 2003

AB The c-Jun NH2-terminal kinase (JNK) group of mitogen-activated protein kinases is stimulated in response to a wide array of cellular stresses and proinflammatory cytokines. Mice lacking individual members of the Jnk family (Jnk1, Jnk2, and Jnk3) are viable and survive without overt structural abnormalities. Here we show that mice with a compound deficiency in Jnk expression can survive to birth, but fail to close the optic fissure (retinal coloboma). We demonstrate that JNK initiates a cytokine cascade of bone morphogenetic protein-4 (BMP4) and sonic hedgehog (Shh) that induces the expression of the paired-like homeobox transcription factor Pax2 and closure of the optic fissure. Interestingly, the role of JNK to regulate BMP4 expression during optic fissure closure is conserved in Drosophila during dorsal closure, a related morphogenetic process that requires JNK-regulated expression of the BMP4 ortholog Decapentaplegic (Dpp).

CC 6-1 (General Biochemistry)

Section cross-reference(s): 3, 12, 13

IT Eye
(retina, embryonic development of; JNK initiates cytokine cascade that causes Pax2 expression and closure of optic fissure)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L640 ANSWER 32 OF 79 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2003:107067 HCAPLUS
 DOCUMENT NUMBER: 138:301885
 TITLE: Aldose reductase mediates cytotoxic signals of hyperglycemia and TNF- α in human lens epithelial cells
 AUTHOR(S): Ramana, Kota V.; Friedrich, Brian; Bhatnagar, Aruni; Srivastava, Satish K.
 CORPORATE SOURCE: Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, Galveston, TX, 77555, USA
 SOURCE: FASEB Journal (2003), 17(2), 315-317, 10.1096/fj.02-0568fje
 CODEN: FAJOEC; ISSN: 0892-6638
 PUBLISHER: Federation of American Societies for Experimental Biology
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 ED Entered STN: 12 Feb 2003
 AB Chronic hyperglycemia and cytokines such as tumor necrosis factor α (TNF- α) cause oxidative stress leading to dysregulated cell growth or apoptosis that contributes to the development of inflammation and secondary complications of diabetes. However, the mechanisms regulating hyperglycemic or cytokine injury are not well understood. Herein we report that inhibition of the polyol pathway enzyme aldose reductase (AR) by two structurally unrelated inhibitors-sorbinil and tolrestat-prevents, in the human lens epithelial cell line B-3, the apoptosis and activation of caspase-3 caused by exposure to high glucose levels or TNF- α . Inhibition of AR attenuated TNF- α and hyperglycemia-induced activation of protein kinase C (PKC), phosphorylation of the inhibitory subunit of nuclear factor- κ B (NF- κ B), and stimulation of NF- κ B, but it did not prevent the activation of NF- κ B and PKC by phorbol ester. Inhibition of AR also attenuated the increase in p38 mitogen-activated protein kinase and c-Jun N-terminal kinase phosphorylation. These signaling pathways were also inhibited in cells in which the expression of AR was reduced by antisense ablation. Collectively, these results identify a new participant in apoptotic signaling and suggest that AR is an obligatory mediator of the apoptotic events upstream of PKC. These observations could provide new insights into the pathophysiol. of diabetes and the role of aberrant glucose metabolism in apoptotic cell death.
 CC 14-8 (Mammalian Pathological Biochemistry)
 Section cross-reference(s): 15
 ST aldose reductase TNF α NF κ B hyperglycemia eye lens epithelium apoptosis
 IT Apoptosis
 Cataract
 Diabetes mellitus
 Human
 Hyperglycemia
 Oxidative stress, biological
 Polyol pathway
 Signal transduction, biological
 (aldose reductase mediates cytotoxic signals of hyperglycemia and TNF- α in human lens epithelial cells)
 IT **Eye, disease**
 (diabetic retinopathy; aldose reductase mediates cytotoxic signals of hyperglycemia and TNF- α in human lens epithelial cells)
 IT **Eye**
 (lens, epithelium; aldose reductase mediates cytotoxic signals of

hyperglycemia and TNF- α in human lens epithelial cells)
 IT 9028-31-3, Aldose reductase 141436-78-4, Protein kinase C 155215-87-5,
c-Jun N-terminal kinase
 165245-96-5, p38 Mitogen-activated protein kinase
 RL: ADV (Adverse effect, including toxicity); BSU (Biological study,
 unclassified); BIOL (Biological study)
 (aldose reductase mediates cytotoxic signals of hyperglycemia and
 TNF- α in human lens epithelial cells)
 REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib ab hitstr 33-37

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE,
 BIOSIS, TOXCENTER, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L640 ANSWER 33 OF 79 USPATFULL on STN

ACCESSION NUMBER: 2005:215554 USPATFULL
 TITLE: Compounds and compositions as protein kinase inhibitors
 INVENTOR(S): Ding, Qiang, San Diego, CA, UNITED STATES
 Xie, Yongping, San Diego, CA, UNITED STATES
 Gray, Nathanael S., San Diego, CA, UNITED STATES
 You, Shuli, San Diego, CA, UNITED STATES
 Chopiuk, Greg, San Diego, CA, UNITED STATES
 Jiang, Jiqing, San Diego, CA, UNITED STATES
 Liu, Yi, San Diego, CA, UNITED STATES
 Steensma, Ruo, La Jolla, CA, UNITED STATES
 Wang, Xing, San Diego, CA, UNITED STATES
 Sim, Taebo, San Diego, CA, UNITED STATES
 PATENT ASSIGNEE(S): IRM LLC, Hamilton, BERMUDA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005187230	A1	20050825
APPLICATION INFO.:	US 2004-961646	A1	20041008 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-509572P	20031008 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	GENOMICS INSTITUTE OF THE, NOVARTIS RESEARCH FOUNDATION, 10675 JOHN JAY HOPKINS DRIVE, SUITE E225, SAN DIEGO, CA, 92121-1127, US	
NUMBER OF CLAIMS:	8	
EXEMPLARY CLAIM:	1	
LINE COUNT:	2392	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides a novel class of compounds, pharmaceutical
 compositions comprising such compounds and methods of using such
 compounds to treat or prevent diseases or disorders associated with
 abnormal or deregulated kinase activity, particularly diseases or
 disorders that involve abnormal activation of the Abl, BCR-Abl, CSK,
 JNK1, JNK2, PDGF-R, p38, p70S6K, TGF β , SRC, EGFR, c-Kit, trkB,
 FGFR3, Fes, Lck, Syk, RAF, MKK4, MKK6 and SAPK2 β kinases.

IT 289898-51-7, Jnk1 kinase
 (preparation of [1,6]naphthyridin-3-ones as protein kinase inhibitors)
 RN 289898-51-7 USPATFULL

Audet 10/650,006

JNK-7's

4/6

Generally (spec)

09/29/2005

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L640 ANSWER 34 OF 79 USPATFULL on STN

ACCESSION NUMBER: 2005:124996 USPATFULL

TITLE: Methods of treating diseases and disorders by targeting multiple kinases

INVENTOR(S): Narla, Rama Krishna, San Diego, CA, UNITED STATES
Sakata, Steven, San Diego, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005107386	A1	20050519
APPLICATION INFO.:	US 2004-994093	A1	20041119 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-523859P	20031119 (60)
	US 2003-608929P	20031119 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017, US	
NUMBER OF CLAIMS:	15	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	3 Drawing Page(s)	
LINE COUNT:	5056	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is directed to the use of single agents, which are compounds that target two or more kinases simultaneously, thus substantially avoiding resistance to therapy. The invention provides methods for the use for, administration to, and treatment of individuals having a variety of diseases or conditions associated with the activity of two or more kinases, comprising administration of one or more single agents, either alone or in combination with other therapies for the same disease or condition.

IT 289898-51-7, JNK1 kinase

(treating diseases and disorders by targeting multiple kinases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA
INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L640 ANSWER 35 OF 79 USPATFULL on STN

ACCESSION NUMBER: 2004:307785 USPATFULL

TITLE: Modulators of telomere stability

INVENTOR(S): Schneider, Michael D., Houston, TX, UNITED STATES
Oh, Hidemasa, Houston, TX, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004242461	A1	20041202
APPLICATION INFO.:	US 2004-820583	A1	20040408 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-461095P	20030408 (60)
DOCUMENT TYPE:	Utility	

FILE SEGMENT: APPLICATION
 LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI, LLP, 1301 MCKINNEY, SUITE 5100,
 HOUSTON, TX, 77010-3095

NUMBER OF CLAIMS: 30
 EXEMPLARY CLAIM: 1
 NUMBER OF DRAWINGS: 34 Drawing Page(s)
 LINE COUNT: 4939

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention embodies methods of modulating telomere repeat-binding factor-2 (TRF2) or cell cycle checkpoint kinase 2 (Chk2) to enhance the survival of a cell. More particularly, the modulators can be used to treat cardiovascular disease by improving the growth and survival of cardiomyocytes.

IT 289898-51-7, JNK1 kinase
 (methods of identifying modulators for telomere stability in treatment of cardiovascular diseases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L640 ANSWER 36 OF 79 USPATFULL on STN

ACCESSION NUMBER: 2004:144533 USPATFULL

TITLE: Method of determining tumor characteristics by determining abnormal copy number or expression level of lipid-associated genes

INVENTOR(S): Skinner, Michael K., Pullman, WA, UNITED STATES
 Patton, Jodi L., Pullman, WA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004110197	A1	20040610
APPLICATION INFO.:	US 2003-647426	A1	20030826 (10)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 2000-676052, filed on 28 Sep 2000, ABANDONED		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	BAKER + HOSTETLER LLP, WASHINGTON SQUARE, SUITE 1100, 1050 CONNECTICUT AVE. N.W., WASHINGTON, DC, 20036-5304		
NUMBER OF CLAIMS:	23		
EXEMPLARY CLAIM:	1		
LINE COUNT:	3825		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of assessing tumor characteristics in tissue samples by determining the copy number or expression level of genes associated with lipid metabolism, synthesis, or action is provided. Gene copy number may be assessed directly from chromosomal material or by determining the expression level of the gene in a tissue sample. The use of physical platforms comprising immobilized nucleic acid polymers to determine copy number or expression level of lipid associated genes by hybridization techniques is also provided.

IT 289898-51-7, JNK1 kinase
 (lipid regulation of expression of gene for; tumor characterization by anal. of expression and copy number of genes involved in lipid metabolism and function)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

L640 ANSWER 37 OF 79 USPATFULL on STN

ACCESSION NUMBER: 2004:39281 USPATFULL

TITLE: Antisense oligonucleotide compositions and methods for the modulation of JNK proteins

INVENTOR(S): McKay, Robert, Poway, CA, UNITED STATES
 Dean, Nicholas M., Olivenhain, CA, UNITED STATES
 Monia, Brett P., Encinitas, CA, UNITED STATES
 Nero, Pamela S., San Diego, CA, UNITED STATES
 Gaarde, William A., Carlsbad, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004029823	A1	20040212
APPLICATION INFO.:	US 2003-345444	A1	20030115 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 2001-774809, filed on 31 Jan 2001, PENDING Continuation-in-part of Ser. No. US 1999-396902, filed on 15 Sep 1999, ABANDONED Continuation-in-part of Ser. No. US 1999-287796, filed on 7 Apr 1999, GRANTED, Pat. No. US 6133246 Continuation-in-part of Ser. No. US 1998-130616, filed on 7 Aug 1998, GRANTED, Pat. No. US 6221850 Continuation-in-part of Ser. No. US 1997-910629, filed on 13 Aug 1997, GRANTED, Pat. No. US 5877309		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Jane Massey Licata, LICATA & TYRRELL P.C., 66 E. Main Street, Marlton, NJ, 08053		
NUMBER OF CLAIMS:	49		
EXEMPLARY CLAIM:	1		
LINE COUNT:	4987		
CAS INDEXING IS AVAILABLE FOR THIS PATENT.			

AB Compositions and methods for the treatment and diagnosis of diseases or disorders amenable to treatment through modulation of expression of a gene encoding a Jun N-terminal kinase (JNK protein) are provided. Oligonucleotide are herein provided which are specifically hybridizable with nucleic acids encoding JNK1, JNK2 and JNK3, as well as other JNK proteins and specific isoforms thereof. Methods of treating animals suffering from diseases or disorders amenable to therapeutic intervention by modulating the expression of one or more JNK proteins with such oligonucleotide are also provided. Methods for the treatment and diagnosis of diseases or disorders associated with aberrant expression of one or more JNK proteins are also provided. Methods for inducing apoptosis and for treating diseases or conditions associated with a reduction in apoptosis are also provided.

IT 289898-51-7, Jun N-terminal kinase 1
 (antisense oligonucleotides for inhibition of c-jun protein N-terminal kinase mRNA for treatment of prostate cancer, inflammation and fibrotic diseases)

RN 289898-51-7 USPATFULL

CN Kinase (phosphorylating), gene c-jun protein N-terminal, 1 (9CI) (CA INDEX NAME)

STRUCTURE DIAGRAM IS NOT AVAILABLE

=> d iall abeq tech abex 38-48

YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

L640 ANSWER 38 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-591917 [60] WPIX
 DOC. NO. CPI: C2005-178393
 TITLE: Increasing Th2 cytokine levels useful for reducing inflammation, comprises providing inhibitor of Itchy homolog E3 ubiquitin protein ligase or kinase inhibitor (mitogen-activated protein kinase kinase kinase 1 or c-Jun N-terminal kinase 1).
 DERWENT CLASS: B04 D16
 INVENTOR(S): GAO, M; KARIN, M; LABUDA, T
 PATENT ASSIGNEE(S): (REGC) UNIV CALIFORNIA
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005079458	A2	20050901	(200560)*	EN	103	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT							
KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG							
ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005079458	A2	WO 2005-US5066	20050217

PRIORITY APPLN. INFO: US 2004-546540P 20040219

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2005079458 A UPAB: 20050920

NOVELTY - Increasing (M1) Th2 cytokine levels produced by T cells comprises providing (i) an inhibitor of ITCH or a kinase inhibitor, where the kinase is mitogen-activated protein kinase kinase kinase 1 (MEKK1) or c-Jun N-terminal kinase 1 (JNK1), (ii) T cells, and (iii) test agent.

DETAILED DESCRIPTION - Increasing (M1) Th2 cytokine levels produced by T cells comprises:

(a) providing (i) an inhibitor of ITCH or a kinase inhibitor, where the kinase is MEKK1 or JNK1, (ii) T cells, and (iii) test agent;

(b) contacting the T cells in the presence of the test agent to produce contacted T cells and in the absence of the test agent to produce control T cells; and

(c) detecting reduced activity of ITCH in the contacted T cells compared to ITCH or to the kinase in the control T cells, where the detecting identifies the test agent as increasing Th2 cytokine levels produced by T cells.

INDEPENDENT CLAIMS are also included for:

(1) identifying (M2) a test agent as reducing the level of differentiation of T cells into TH1 cells;

(2) inflammation (M3) and disease associated with TH1 cell abundance

by increasing the in vivo production of Th2 cells;

(3) a composition comprising a transgenic mouse that comprises MEKK1-/MEKK1- or MEKK1-/MEKK1+;

(4) identifying (M4) therapeutic agents that are useful in reducing one or more of MEKK-MEKK4/MKK7-JNK-ITCH cascade pathway activity and direct MEKK1-ITCH protein to protein interactions; and

(5) a method where the JNK inhibitor comprises SP600125.

ACTIVITY - Antiinflammatory; Neuroprotective; Antidiabetic; Antithyroid; Antirheumatic; Antiarthritic; Immunomodulator.

No biological data given.

MECHANISM OF ACTION - Protein kinase inhibitor.; ITCH inhibitor; Itchy homolog E3 ubiquitin protein ligase inhibitor; MEKK-1 protein kinase inhibitor; Jun N terminal kinase inhibitor; MEKK-4 protein kinase inhibitor; MKK-7 alpha protein kinase inhibitor; Antisense oligonucleotide inhibitor; RNAi; RNA interference.

USE - The method is useful for increasing Th2 cytokine levels produced by T cells. Especially the method is useful for reducing inflammation and disease, where the disease is multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, or rheumatoid arthritis.

Dwg.0/18

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; DCN

MANUAL CODES: CPI: B04-F04; B04-G02; B04-G03; B04-L04C; B04-L08; B04-M01; B04-N02; B04-P0100E; B06-D18; B11-C08E3; B11-C08E7; B12-K04E1; B14-C03; B14-C09B; B14-D06C; B14-D10; B14-G02D; B14-G03; B14-N11; B14-S01; B14-S03B; B14-S03C; B14-S04; D05-A02B; D05-A02F; D05-H09; D05-H11; D05-H16A

TECH UPTX: 20050920

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The method of (M1) further comprises identifying the test agent as increasing the level of one or more of Th2 cytokine or identifying the test agent as decreasing the level of TH1 cytokines. The kinase inhibitor preferably comprises SB600125.

Alternatively, the method comprises providing (i) T cells and (ii) agent that reduces activity of an ITCH or agent that reduces activity of a kinase, where the kinase is MEKK1 or JNK 1, and contacting the T cells with the agent where the agent reduces the activity of the ITCH or of the kinase.

The method further comprises identifying the test agent as increasing the level of IL-10 produced by the T cells. The T cells are inflammatory disease T cells.

Increasing Th2 cytokine levels produced by T cells comprises reducing the activity of an ITCH, of a MEKK1, or of a JNK1. Specifically, increasing Th2 cytokine levels produced by pro-inflammatory disease T cells comprises providing (i) pro-inflammatory disease T cells, and (ii) agent that reduces activity of an ITCH, and contacting the pro-inflammatory disease T cells with the agent under conditions such that the agent increases the level of interleukin (IL)-10 produced by the T cells.

In (M2) the method comprises reducing MEKK1 catalytic activity in the T cells. Reduction of the MEKK1 catalytic activity comprises increasing the level of differentiation of the T cells into Th2 cells. Reducing of the MEKK1 catalytic activity comprises increasing the level of one or more Th2 cell cytokine that is produced by the T cells, where the increased level of the Th2 cytokine occurs in the absence of an increase in the level of one or more Th1 cytokine, where the Th1 cytokine is interferon-gamma or IL-2. The Th2 cytokine is IL-4, IL-5, IL-10, or IL-13. Increasing the level of the Th2 cell cytokine comprises increasing the level of mRNA encoding the Th2 cytokine, where the mRNA encoding the Th2 cytokine is increased 5-fold. Reducing of the MEKK1 catalytic activity comprises

increasing the level of proliferation of Th2 cells that differentiate from the T cells. Reducing of the MEKK1 catalytic activity comprises introducing a mutation in the gene encoding MEKK1. The T cells comprise thymocyte cells or splenocyte cells. The T cells are in vitro or are in vivo in an animal, where the animal is human. The human is suspected or is not suspected of having a TH1-mediated disease, or suspected of being capable or not capable of developing a TH1-mediated disease. The method comprises one or more of: identifying the agent as increasing the level of differentiation of the T cells into Th2 cells, identifying the agent as increasing the level of one or more Th2 cell cytokine that is produced by the T cell, or identifying the agent as increasing the level of proliferation of Th2 cells that differentiate from the T cells. Alternatively, the method comprises providing a test agent and MEKK1, contacting the test agent and the MEKK1, and detecting reduced MEKK1 kinase activity in the presence of the agent compared to in the absence of the agent, thus identifying the test agent as causing one or more of increasing Th2 cells, decreasing the level of TH1 cells, and decreasing TH1 disease.

The method of (M3) comprises reducing one or more of MEKK1-MEKK4/MKK7-JNK-ITCH cascade pathway activity and direct MEKK1-ITCH protein to protein interactions, where the disease is multiple sclerosis, type 1 diabetes, autoimmune thyroiditis, or rheumatoid arthritis.

Reducing comprises using one or more MEKK1 enzyme inhibitors, where the enzyme inhibitors comprise SP600125. Reducing comprises using one or more neutralizing antibodies that specifically bind to MEKK1. Reducing is achieved by reducing expression of the MEKK1 gene.

Reducing comprises using one or more MEKK4/MKK7 enzyme inhibitors, where the MEKK4/MKK7 enzyme inhibitors comprise SP600125. Reducing comprises neutralizing antibodies that specifically bind to MEKK4/MKK7. Reducing comprises inhibiting expression of the MEKK4/MKK7 gene.

Reducing comprises using ITCH enzyme inhibitors. Reducing comprises using neutralizing antibodies that specifically bind to ITCH. Reducing comprises inhibiting the expression of the ITCH gene.

The expression of a JNK, MEKK1, MEKK4/MKK7, or ITCH gene is suppressed by the use of one or more of RNAi, and antisense molecules. The neutralizing antibody is chosen from human antibody and humanized antibody that invoke minimum and therapeutically acceptable level of immunogenic defense response in a human. The MEKK1-ITCH interactions are reduced by using SP600125.

The MEKK1-ITCH interactions are reduced by the use of neutralizing antibodies against one or more of MEKK1, MEKK4 and ITCH.

(M4) comprises providing (i) WT and MEKK1KD thymocytes stimulated with, (ii) anti-CD3, (iii) anti-CD28 for 24 hrs, and (iv) in the absence or presence (0.5 mM) cfa JNK inhibitor, preparing cell lysates from the thymocytes, immunoblotting the lysates, and determining levels of one or more of ITCH, c-Jun and JunB to identify therapeutic agents that are useful in reducing cascade pathway activity.

L640 ANSWER 39 OF 79	WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER:	2005-386200 [39] WPIX
DOC. NO. CPI:	C2005-119453
TITLE:	New vascular endothelial growth factor receptor (VEGFR) antagonist comprising immunoglobulin-like domains 4-7 or 5-7 or its functional variants, useful for treating cancer and non-neoplastic diseases e.g. psoriasis.
DERWENT CLASS:	B04 D16
INVENTOR(S):	CHEN, W Y; PARK, J P
PATENT ASSIGNEE(S):	(GREE-N) GREENVILLE HOSPITAL SYSTEM
COUNTRY COUNT:	108
PATENT INFORMATION:	

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005046602	A2	20050526	(200539)*	EN	42	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT							
KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM							
ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							
US 2005196396	A1	20050908	(200559)			A61K039-395	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005046602	A2	WO 2004-US37381	20041110
US 2005196396	A1 Provisional	US 2003-518295P	20031110
		US 2004-985013	20041110

PRIORITY APPLN. INFO: US 2003-518295P 20031110; US
2004-985013 20041110

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K039-395
SECONDARY: C07K016-22

BASIC ABSTRACT:

WO2005046602 A UPAB: 20050621

NOVELTY - A vascular endothelial growth factor receptor (VEGFR) antagonist that comprises immunoglobulin-like domains 4-7 or 5-7 or its functional variants, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

- (1) a fusion protein comprising a VEGF receptor antagonist and at least one domain selected from prolactin receptor antagonizing domain, a cytokine, a VEGF ligand and a combination of those;
- (2) a polynucleotide encoding a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 from a VEGFR;
- (3) a vector comprising the polynucleotide;
- (4) a host cell transformed with the vector;
- (5) a method of treating a cancer;
- (6) a method of decreasing angiogenesis;
- (7) a method for making a VEGF receptor antagonist;
- (8) a method for slowing the progression of a cancer; and
- (9) a cell based assay system for identifying a test compound capable of inducing VEGFR activity.

ACTIVITY - Cytostatic; Antirheumatic; Antiarthritic; Antipsoriatic; Antiarteriosclerotic; Antidiabetic; **Ophthalmological**; Antithyroid; Antiinflammatory; Respiratory-Gen.; Nephrotropic; Gynecological; Cardiant.

MECHANISM OF ACTION - VEGFR-Antagonist. T-47D cells were cultured overnight in serum free media at 80% confluency and were treated for 60 minutes with G129R and KDR (Ig4-7) as compared to untreated cells. Membranes were stripped and re-probed with anti-mitogen activated protein kinase (MAPK) antibody to ensure equal loading. Results indicated that MAPK phosphorylation decreased in the presence of KDR (Ig4-7) compared to control samples indicating that KDR (IG4-7) blocks the ability of a full length KDR monomer to form a

functional homodimer and effect VEGF signaling.

USE - The VEGFR antagonist is useful for treating neoplastic diseases and disorders such as carcinomas of the breast, lung, esophagus, gastric anatomy, colon, rectum, liver, ovary, cervix, endometrium, thecomas, arrhenoblastomas, endometrial hyperplasia, endometriosis, fibrosarcomas, choriocarcinoma, head and neck cancer, nasopharyngeal carcinoma, laryngeal carcinoma, hepatoblastoma, Kaposi's sarcoma, melanoma, skin carcinomas, hemangioma, cavernous hemangioma, hemangioblastoma, pancreas carcinoma, retinoblastoma, astrocytoma, glioblastoma, Schwannoma, oligodendroglioma, medulloblastoma, neuroblastomas, rhabdomyosarcoma, osteogenic sarcoma, leiomyosarcomas, urinary tract carcinomas, thyroid carcinomas, Wilm's tumor, renal cell carcinoma, prostate carcinoma, abnormal vascular proliferation associated with phakomatoses, edema (such as associated with brain tumors), and Meigs' syndrome; and non-neoplastic conditions such as rheumatoid arthritis, psoriasis, atherosclerosis, diabetic and other retinopathies, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, thyroid hyperplasias (including grave's disease), corneal and other tissue transplantation, chronic inflammation, lung inflammation, nephrotic syndrome, preeclampsia, ascites, pericardial effusion (such as associated with pericarditis) and pleural effusion.

Dwg.0/9

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB

MANUAL CODES: CPI: B04-E02A; B04-E08; B04-F0100E; B04-G04; B04-N08;
B11-C08E1; B12-K04E1; B14-C03; B14-C09B; B14-D01C;
B14-F02F2; B14-F07; B14-G02C; B14-H01; B14-L06;
B14-N03; B14-N14; B14-N17C; B14-S03A;
D05-H09; D05-H12A; D05-H12E; D05-H14; D05-H17C1

TECH UPTX: 20050621

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation (claimed): Making a VEGFR antagonist comprises introducing an expression vector encoding a VEGF receptor antagonist into an expression system and effecting expression of the VEGF receptor antagonist. At least one immunoglobulin-like domain is from kinase domain receptor (KDR). The VEGFR antagonist comprises immunoglobulin-like domains 4-7 from KDR,flt-1, FLT4, platelet derived growth factor (PDGF), and combinations of those. It is a KDR (Ig4-7), and can form heterodimers with a VEGFR selected from KDR,flt-1, FLT4 and PDGF. It is optionally formulated in a pharmaceutical excipient. The prolactin receptor antagonizing domain is G129R. The fusion protein comprises a VEGF receptor antagonist and a VEGF ligand. 10. The VEGF receptor antagonist is a chimeric VEGF receptor antagonist. The KDR is encoded by the sequence comprising fully defined 1281 bp (SEQ ID NO: 1) given in the specification.

Preferred Method: Treating cancer comprises administering a polynucleotide encoding:

(a) a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7; or

(b) a fusion protein comprising a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7, and a domain selected from a prolactin receptor antagonizing domain, a VEGF ligand, a cytokine, and a combination of those.

The cancer is breast cancer. The prolactin receptor antagonizing domain is G129R. The method may comprise:

(a) administering a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7, or a fusion protein comprising a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7, and a domain selected from a prolactin receptor antagonizing domain, a VEGF ligand, a cytokine, and a combination of those; and

(b) inhibiting or substantially inhibiting the VEGF signal transduction

cascade.

Decreasing angiogenesis comprises administering a polynucleotide encoding:
(a) a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7; or
(b) a fusion protein comprising a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7.

The method may comprise:

(a) administering a VEGF receptor antagonist comprising immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7, or a fusion protein comprising a VEGF receptor antagonist that comprises immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7; and
(b) inhibiting formation of tumor neovasculature.

Slowing the progression of a cancer comprises:

(a) administering a VEGF receptor antagonist comprising immunoglobulin-like domains 4-7 or immunoglobulin-like domains 5-7, or a fusion protein comprising a VEGF receptor antagonist; and
(b) slowing cell proliferation in the target cell.

The fusion protein further comprises at least one domain selected from a VEGF ligand, a prolactin receptor antagonizing domain, a cytokine and a combination of those. The vector further comprises a nucleic acid encoding at least one of the following selected from a prolactin receptor antagonizing domain, a VEGF ligand and a cytokine.

Identifying a test compound capable of inducing VEGFR activity comprises:

(i) contacting a test compound to a cell that expresses the prolactin receptor, in the presence and absence of a compound that substantially inhibits VEGF mediated cell proliferation;

(ii) measuring the level of proliferation in the cell in the presence and absence of the compound that substantially inhibits VEGF mediated cell proliferation; and

(iii) comparing the levels of cell proliferation obtained in (ii).

The compound that substantially inhibits VEGF mediated cell proliferation is KDR (Ig4-7) or KDR (Ig5-7). At least one of the immunoglobulin-like domains is from one VEGF receptor and at least one of the immunoglobulin-like domains is from a different VEGFR.

ABEX

UPTX: 20050621

ADMINISTRATION - Dosage can be 1-10 mg/kg. Administration can be done by inhalation or insufflation, or oral, buccal, parenteral or rectal means.
EXAMPLE - BL21 (DE3) cells were transformed with plasmids encoding recombinant proteins using a calcium chloride method. The transformants were spread on an ampicillin plate, and grown overnight at 37degreesC. The LB seed culture was inoculated and grown overnight. The following day a LB growth culture was generated by inoculation of 5% of the seed culture and grown for approximately 2.5 hours at 37degreesC with agitation. IPTG was added to the culture to induce expression of recombinant proteins and incubated for an additional 4 hours. Bacteria was pelleted and resuspended in a solution, the resuspended bacteria was lysed, and the products, which were in the form of inclusion bodies, were pelleted and resuspended in NaPO4 (0.2M; pH 7), beta mercaptoethanol (1% v/v), and Urea (8M) for refolding. The refolding process consisted of dialyzing the protein against decreasing amounts of urea and beta-mercaptoethanol in the presence of NH4HCO3 (50 mM; pH 8.0) for 3 consecutive days. The sample was then purified by a Q-Sepharose anionic exchange column using a fast performance liquid chromatography system.

L640 ANSWER 40 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-273043 [28] WPIX

CROSS REFERENCE: 2003-712583 [67]

DOC. NO. CPI: C2005-085327

TITLE: New conjugates of biologically active compounds for treating e.g. inflammatory disorders, infectious

diseases, cancer, allergy and immune disorders, contain a transportophore, a bond or linker and a non-antibiotic therapeutic agent.

DERWENT CLASS: B02 B03

INVENTOR(S): BECK, A; BURNET, M; EGGERS, M; FLOHR, C; GUSE, J; GUTKE, H; KHOBZAQUI, M; MARGUTTI, S

PATENT ASSIGNEE(S): (SYNO-N) SYNOVO GMBH

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2005027828	A2	20050331	(200528)*	EN	97	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005027828	A2	WO 2004-US26485	20040816

PRIORITY APPLN. INFO: US 2003-644600 20030820

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2005027828 A UPAB: 20050504

NOVELTY - Conjugates of biologically active compounds are new and contain a transportophore, a bond or linker and a non-antibiotic therapeutic agent.

DETAILED DESCRIPTION - A conjugate compound (I) of biologically active compounds is new. The compound is of formula T-(L-C)m.

T = transportophore;

L = a bond or a linker having a molecular weight up to 240 dalton;

C = a non-antibiotic therapeutic agent; and

m = 1-8;

The transportophore has an immune selectivity ratio of at least 2 and is covalently bonded to the non-antibiotic therapeutic agent via the bond or the linker. The compound has an immune selectivity ratio of at least 2.

ACTIVITY - Antiinflammatory; Antimicrobial; Cytostatic; Antiallergic; Immunomodulator; Vasotropic; Cardiovascular-Gen.; Respiratory-Gen.; Dermatological; Antirheumatic; Hepatotropic.

MECHANISM OF ACTION - Protein kinase inhibitor; Protease inhibitor.

USE - (I) is useful to treat an inflammatory disorder, infectious disease, cancer, allergy or immune disorder (claimed). (I) is also useful to treat diseases such as metabolic cardiovascular, pulmonary, dermatological, rheumatological and hepatic diseases.

ADVANTAGE - (I) improves the ease of formulation, gastric stability, bioavailability, stability, disposition, elimination, half life, efficacy, safety, duration of action and selectivity of the agent. (I) has:

(a) improved uptake across the intestinal, jejunal, duodenal, colonic, or other mucosa;

(b) reduced first pass effect by mucosal oxygenases;

(c) reduced or altered detoxification by degradative enzymes of the

body;

- (d) reduced efflux;
- (e) selective accumulation of the therapeutic agent in one or more immune, fibroblast, hepatic, renal, glial, or other target cells;
- (f) potential for hydrolytic or other forms of separation on a timescale compatible with therapy and the other desired disposition events;
- (g) enhanced pharmacological effect in the target cells through greater concentration, sustained release, reduced substrate competition effect or other mechanisms;
- (h) reduced or modified dose;
- (i) modified route of administration;
- (j) reduced or altered side effects;
- (k) alternative uses; and
- (l) alternative formulations.

Tests details are described but no results given.

Dwg. 0/2

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-H; B07-H; B10-A06; B10-A08; B10-A09B; B10-A11B;
 B10-A15; B10-A16; B10-A17; B10-A18; B10-B01;
 B10-B02; B10-B03; B10-B04; B10-C04; B10-D03;
 B10-E04; B10-F02; B10-G02; B14-A01; B14-A02;
 B14-C01; B14-C03; B14-C06; B14-D02A2; B14-D05D;
 B14-D06C; B14-D07C; B14-F01; B14-F02; B14-F03;
 B14-F04; B14-F06; B14-G02; B14-G02A; B14-G03;
 B14-H01; B14-K01; B14-N17; B14-S13

TECH UPTX: 20050504

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises reaction of a transportophore having a reactive moiety with a therapeutic agent having another reactive moiety. One of the two reactive moieties is a leaving group (e.g. -Cl or OR) and the other is a derivatizable group (e.g. -OH or -NH-). The transporter is covalently bonded to the therapeutic agent via a reaction between the two reactive moieties. When a linker is present, each of the two reactive moieties, is a leaving group or a derivatizable group and each reacts with its reactive counterpart in the linker to form a covalent bond.

Preferred Components: The transportophore is an amphiphilic molecule (having a pKa value of 6.5-9.5) or a cyclic or heterocyclic molecule (preferably a cyclic or heterocyclic molecule having an attached sugar, a macrolactone or macroether having an attached sugar, or a macrolide (mono-, di or tri basic) or a ketolide having an amino sugar).

Preferably, (I) is a macrolide of formula (Ia)-(Id).

In (Ia):

X = N(R7)-CH2, CH2-N(R7), C(=O), C(=NOR8), CH(OR9), CH(NR10R11), C(=NR12), OC(=O) or C(=O)O;

Y = independently linker;

Z = C(=O), CH(R16); either

R1 = H, CH3, 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkenyl, 6-10C aryl-(1-5C alkyl), 2-9C heteroaryl-(1-5C alkyl), (1-4C alkyliden)-NR18R19, Y-R13, C(=O)-Y-R15 or C(=O)-R15;

R2 = H, (1',2'-cis)-OH, (1',2'-trans)-OH, (1',2'-cis)-OR15, (1',2'-trans)-OR15, (1',2'-cis)-SH or (1',2'-cis)-S-Y-R13, (R1 and R2 are connected via a OC(=O)CHR16);

R3, R4 = H, C(=O)-Y-R15 or C(=O)-R15; either

R5 = H; or

R4+R5 = Z;

R6 = H or CH3;

R7 = H, CH3, Y-R13, C(=O)-Y-R15 or C(=O)-R15;

T = 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl,

1-8C(1-4C alkoxy)alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl) (where alkyl, alkenyl, alkynyl, aryl or heteroaryl optionally substituted by 1-5 substituents of halo, 1-4C alkyl, 1-4C alkenyl, 1-4C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, 1-4C alkoxy, OH, NO₂, CN, azido, mercapto, R₁₈R₁₉, R₁₈C(=O), R₁₈C(=O)O, R₁₈OC(=O)O, R₁₈NHC(=O), R₁₈C(=O)NH, R₁₈R₁₉NC(=O) or R₁₈OC(=O));

R₈ = T, H, Y-R₁₃, R₁₃, C(=O)-R₁₇ or (1-4C alkyliden)-NR₁₈R₁₉;

R₉ = T or H;

T₁ = 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl) or (1-4C alkyliden)-NR₁₈R₁₉;

R₁₀ = T₁ or H;

R₁₁ = T₁, H, Y-R₁₃, C(=O)-Y-R₁₅ or C(=O)-R₁₅;

R₁₂ = T₁, H or Y-R₁₃;

R₁₃, R₁₅ = therapeutic agent;

R₁₆ = H, CH₃, 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, (1-8C)(1-4C alkoxy) alkyl, (1-8C)(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl), (2-9C heteroaryl)-(1-5C alkyl), (1-4C alkyliden)-NR₁₈R₁₉ or Y-R₁₃;

R₁₇ = O-R₂₀-aryl (optionally substituted by -(X-a)-Y therapeutic agent;

X-a = therapeutic agent (S, O or NH);

R₁₈, R₁₉ = H, 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl) or (2-9C heteroaryl)-(1-5C alkyl); and

R₂₀ = Halo, 1-3C alkyl, NO₂, CN, OCH₃, N(CH₃)₂, N₃, SH or S(1-4C alkyl).

In (Ib):

R₁ = 2-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkenyl, 6-10C aryl-(1-5C alkyl), 2-9C heteroaryl-(1-5C alkyl), S(=O)_k(1-10C alkyl), S(=O)_k(1-10C alkenyl), S(=O)_k(1-10C alkynyl), S(=O)_k(6-10C aryl), S(=O)_k(2-9C heteroaryl), cycloalkyl, heterocycloalkyl (optionally be substituted by 1-3 halo, CN, OH, 1-4C alkyloxy, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, NR₁₈R₁₉, R₁₈C(=O), R₁₈C(O)O, R₁₈OC(=O), R₁₈C(=O)NH, R₁₈NHC(=O), R₁₈R₁₉NC(=O) or R₁₈OC(=O)), H, CH₃, (1-4C alkyliden)-NR₁₈R₁₉, Y-R₁₃, C(=O)-Y-R₁₅, C(=O)-R₁₅, S(=O)_k-Y-R₁₅ or S(=O)_k-R₁₅;

k = 0-2;

R-3a, R-3b = H, R₁, OH, OR₁₁ or NR₁₀R₁₁;

R₈ = H, Y-R₁₃ or C(=O)-R₁₇;

R₉ = H, 1-10C alkyl, 1-10C alkenyl, 1-10C alkynyl, 1-8C(1-4C alkoxy) alkyl, 1-8C(1-4C alkoxy) alkenyl, (6-10C aryl)-(1-5C alkyl) or (2-9C heteroaryl)-(1-5C alkyl); either

R₁₀, R₁₁ = H, 1-10C alkyl, 1-10C alkenyl, 3-10C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 2-9C heteroaryl (optionally substituted by 1-3 halo, CN, OH, 1-4C alkyloxy, NO₂, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, NR₁₈R₁₉, R₁₈C(=O), R₁₈C(=O)O, R₁₈OC(=O), R₁₈C(O)NH, R₁₈NHC(=O), R₁₈R₁₉NC(=O) or R₁₈OC(=O)-O); or

R₁₀ = H; and

R₁₁ = Y-R₁₃, C(=O)-Y-R₁₅, C(=O)-R₁₅, S(=O)_k(1-10C alkyl), S(=O)_k(1-10C alkenyl), S(=O)_k(1-10C alkynyl), S(=O)_k(6-10C aryl), S(=O)_k(2-9C heteroaryl), S(=O)_k-Y-R₁₅, S(=O)_k-R₁₅, where k is 0-2 and alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl or heteroaryl (all optionally substituted).

In (Ic):

X = N(R₉)-CH₂, CH₂-N(R₉), C(=O), C(=NOR₁₀), C(OR₁₁)H, CH(NR₁₂R₁₃), C(=NR₁₄), OC(=O) or C(=O)O;

Y = linker; either

R₁ = OR₁₇ or NR₁₇R₁₈; or

R₁+OR₄, R₁₀R₅ = lactone; or

R1+R2 = lactone or lactam;
T2 = halo, 1-4C alkyl, 1-4C alkenyl, 1-4C alkynyl, 3-7C cycloalkyl, 1-6C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl, 1-4C alkoxy, OH, NO₂, CN, azido, mercapto, R₂₀R₂₁N, R₂₀C(=O), R₂₀C(=O)O, R₂₀OC(=O), R₂₀NHC(=O), R₂₀C(=O)NH, R₂₀R₂₁NC(O) or R₂₀OC(=O)O, Y-therapeutic agent or therapeutic agent;
R2 = O-2-cladinosyl, H, X-a, azido, NO₂, CN, OR₁₇, OR₂₂, NR₁₇R₁₈, SR₁₇ 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);
X-a = halo;
R3 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);
R4 = O-2-desosaminy, H, C(=O)R₁₇, Y-therapeutic agent, therapeutic agent, S(=O)₂R₁₇ (Provided that R₁₇ is not H), C(=O)NR₁₇R₁₈(1-6C alkyl), 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl or 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), where R4 is connected to R2 containing a N or O by -C(=O), -S(=O)_n, -CR₂₀R₁₇, -CR₂₀ (therapeutic agent) forming in dependence of R2 or 6 or 7 membered ring;
n = 1-2;
R5 = R₂₀ or C(=O)R₂₀, where R4 and R5 is connected by C(=O), -S(=O)_n, -CR₂₀R₁₇, -CR₂₀ (therapeutic agent);
R6, R7, R8 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), -C(=O)R₁₇, Y-therapeutic agent, -therapeutic agent, -S(=O)₂R₁₇ (provided that R₁₇ is not H) or -C(=O)NR₁₇R₁₈, two of each R6, R7, R8 are connected by C(=O), -S(=O)_n, -CR₂₀R₁₇, -CR₂₀ (therapeutic agent);
R9 = H, CH₃, Y-therapeutic agent, therapeutic agent, 1-6C alkyl, 1-6C alkenyl or 1-6C alkynyl (where alkyl, alkenyl, alkynyl are all optionally substituted by 1-5 substituents of T2);
R10 = C(=O)-aryl, therapeutic agent, H, 1-6C alkyl, 1-6C alkenyl or 1-6C alkynyl (where alkyl, alkenyl, alkynyl are optionally substituted by 1-5 substituents of T2);
R11 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl (where alkyl, alkenyl, alkynyl are optionally substituted by 1-5 substituents of T2) or -C(=O)R₁₇;
R12, R13 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2), -C(=O)R₁₇, S(=O)₂R₁₇ (provided that R₁₇ is not H) or -C(=O)NR₁₇R₁₈;
R14, R17, R18 = H, 1-6C alkyl, 1-6C alkenyl, 1-6C alkynyl, 3-10C cycloalkyl, 1-9C heterocycloalkyl, 6-10C aryl, 1-9C heteroaryl (where alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl groups are optionally substituted by 1-5 substituents of T2);
R20, R21 = H or 1-6C alkyl; and
R22 = C(=O)R₁₇, Y-therapeutic agent, therapeutic agent, S(=O)₂R₁₇ providing R₁₇ is not H, or -C(=O)NR₁₇R₁₈.
Provided that connected to a N, R₁₇, R₁₈ may form a cyclic structure of 4-7 members (including the nitrogen).
In (Id):
m = 0-3;
n = 0-7;

X = O, S, Se, NR1 or PR1 (provided that at least one X is NR1);
 A = CH2, CHR2, CR2R3 or C(=O) (provided that at least one X is -NR1- is not an amide);
 k = 0-2;
 R1 = H, 1-10C alkyl, optionally substituted by F, CN, R4, R4O2C, R4C(=O)NH or R4S(=O)k, R4C(=O) or R4S(=O)k;
 R2, R3 = NH2, NHR1, NR1R5, OH, OR4, R4C(=O) (1-6C alkyl), 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl (1-6C alkyl), 2-9C heterocycloalkyl (1-6C alkyl), 6-10C aryl (1-6C alkyl) or 2-9C heteroaryl (1-6C alkyl), where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substitutes of T3;
 T3 = halo, 1-4C alkoxy, OH, nitro, CN, -C(=O)-OR8, -C(O)N(H)R8, 6-10C aryl, 2-9C heteroaryl, NasteriskR5R6R7 wherein asterisk is no or a positive charge, one or two of R2, R3 can be a directly coupled therapeutic agent;
 R4 = NH2, NHR9, NR9R5, OH, OR9, 1-6C alkyl, 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl (1-6C alkyl), 2-9C heterocycloalkyl (1-6C alkyl), 6-10C aryl (1-6C alkyl) or 2-9C heteroaryl (1-6C alkyl), (where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substituents of T3;
 R5, R6 = H, 1-6C optionally substituted by OH, 6-10C aryl or 2-9C heteroaryl;
 R7 = lone electron pair, CH3, C2H5, C3H7 or CH2-C6H5;
 R8 = therapeutic agent; and
 R9 = 1-6C alkyl, 2-12C alkenyl, 2-12C alkynyl, 3-10C cycloalkyl (1-6C alkyl), 2-9C heterocycloalkyl (1-6C alkyl), 6-10C aryl (1-6C alkyl) or 2-9C heteroaryl (1-6C alkyl), where the alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl and (hetero)aryl groups are optionally substituted by 1-3 substituents of T3.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compound: The non-antibiotic therapeutic agent is an anti-inflammatory agent (preferably a protein kinase inhibitor, a protease inhibitor or an 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitor); an anti-infectious agent (preferably a protease inhibitor); an anti-cancer agent; a fluorescent molecule useful in diagnostic or exploratory applications; an immune-suppressant agent (preferably an analog of vitamin D or a statin); or an agent for treating a hematopoietic disorder, metabolic disease, excessive coagulation or hypercholesterolemia.

ABEX

UPTX: 20050504

ADMINISTRATION - Administration of (I) is 0.1-20 mg/kg, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, subcutaneously, orally, buccally, nasally, transmucosally, topically, ocularly or by inhalation.

EXAMPLE - A solution of simvastatin (420 mg) in dichloromethane (3 ml) was treated with succinic anhydride (110 mg) and 4-(dimethylamino)pyridine (DMAP) (10 mg). After 36 hours, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (210 mg) and drug carrier of formula (2) (600 mg) was added under stirring. After 1 hour, the mixture was passed through a pad of silica gel, eluting with chloroform:isopropanol:methanolic ammonia (30:1:1) to yield macrolide of formula (4) as an off white solid (440 mg; 40% yield).

DEFINITIONS - Preferred Definitions: In (I),
 L = 1-8C alkyl, 1-8C alkenyl, 1-8C alkynyl, 3-10C cycloalkyl, 6-10C aryl, 2-9C heteroalkyl or 2-9C heteroaryl, where the alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heteroaryl spacing elements are optionally substituted by 1-6C alkyl, 1-4 halogens, 1-4C alkoxy, 1-4C alkoxycarbonyl, OH, amino, 1-4C (di)alkylamino, 3-10C cycloalkyl, 1-6C alkylcarbonyloxy, 1-6C alkylcarbonylamido, 1-4C (di)alkylamio carbonyl, nitro, CN, 1-4C

alkylimino, mercapto or 1-4C alkylmercapto.

L640/ANSWER 41 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-496648 [50] WPIX
 DOC. NO. CPI: C2005-151027
 TITLE: New benzimidazol-2-yl-methyl phenylcarbamate compounds
 useful for the treatment of hyperproliferative disorders
 e.g. cancer, benign hyperplasia of the skin or prostate.
 DERWENT CLASS: B02
 INVENTOR(S): JOHNSON, T O; KELLUM, J H; RUI, E Y
 PATENT ASSIGNEE(S): (AGOU-N) AGOURON PHARM INC
 COUNTRY COUNT: 1
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2005148643	A1	20050707	(200550)*		58	A61K031-43	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005148643	A1 Provisional	US 2003-496659P	20030819
		US 2004-922337	20040819

PRIORITY APPLN. INFO: US 2003-496659P 20030819; US
 2004-922337 20040819

INT. PATENT CLASSIF.:

MAIN: A61K031-43
 SECONDARY: A61K031-4184; A61K031-4188; C07D277-60; C07D277-84;
 C07D498-02

BASIC ABSTRACT:

US2005148643 A UPAB: 20050805
 NOVELTY - Benzimidazol-2-yl-methyl phenylcarbamate compounds (I) are new.
 DETAILED DESCRIPTION - Benzimidazol-2-yl-methyl phenylcarbamate
 compounds of formula (I) and their prodrugs, pharmaceutically active
 metabolites, solvates and salts are new.
 R1 = (1-6C)alkyl, -di(1-6C)alkyl-amino, (1-6C)alkyl-amino,
 (1-6C)alkoxy (all optionally substituted by 1-3 Y1), -OH or -NH2;
 Y1 = halo, azido, nitro, -OH, -NH2, -di(1-6C)alkyl-amino,
 -(1-6C)alkyl-amino, (3-6C)cycloalkyl or (1-6C)alkoxy;
 R2-R10 = H, nitro, halo, azido, -NR12aR12b, -NR12aSO2R12b,
 -NR12aC(O)R12b, -OC(O)R12aR12b (sic), -NR12aC(O)OR12b, -OC(O)NR12aR12b,
 -SR12a, S(O)R12a, -SO2R12a, -SO3R12a, -SO2NR12aR12b, -COR12a, -CO2R12a,
 -CONR12aR12b, -(1-4C)perfluoroalkyl, -(CR13R14)tCN, and T1;
 T1 = -(CR13R14)t-aryl, -(CR13R14)t-heterocycle, (2-6C)alkynyl,
 -(CR13R14)r-(3-6C)cycloalkyl, (2-6C)alkenyl, or (1-6C)alkyl (all
 optionally substituted by 1-3 Y2);
 t,u = 0 - 3; or
 R7+R8, R8+R9, R2+R3, R3+R4 = aryl, (5-6C)cycloalkyl, monocyclic
 heterocycle (all optionally substituted by 1-3 Y2), -C(O)-O-(CR13R14)t or
 -O(CR13R14)tO-;
 R11 = H;
 R12a, R12b = H, or T2;
 T2 = -(CR13R14)u-(3-6C)cycloalkyl, -(CR13R14)u-aryl,
 -(CR13R14)u-heterocycle- or (1-6C)alkyl (all optionally substituted by 1-3
 Y3);
 R13, R14 = H, F, or (1-6C)alkyl; or
 R13+R14 = carbocycle; or

R13+R13 = carbocycle;
 Y2,Y3 = halo, cyano, nitro, tetrazolyl, guanidino, amidino, methylguanidino, azido, C(O)Z1, -CF3, -CF2CF3, -CH(CF3)2, -C(OH)(CF3)2, -OCF3, -OCF2H, -OCF2CF3, -OC(O)NH2, -OC(O)NHZ1, -OC(O)NZ1Z2, -NHC(O)Z1, -NHC(O)NH2, -NHC(O)NHZ1, -NHC(O)NZ1Z2, -C(O)OH, -C(O)OZ1, -C(O)NH2, -C(O)NHZ1, -C(O)NZ1Z2, -P(O)3H2, -P(O)3(Z1)2, -S(O)3H, -S(O)m-Z1, -Z1, -OZ1, -OH, -NH2, -NHZ1, -NZ1Z2, -C(=NH)NH2, -C(=NOH)NH2, -N-morpholino, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)haloalkyl, (2-6C)haloalkenyl, (2-6C)haloalkynyl, (1-6C)haloalkoxy, -(CZ3Z4)rNH2, -(CZ3Z4)rNHZ1, -(CZ3Z4)rNZ1Z2 or -S(O)m(CF2)qCF3;
 m = 0 - 2;
 q = 0 - 5;
 r = 1 - 4;

Z1,Z2 = t1 or 3-8C cycloalkyl;
 t1 = 1-12C alkyl, 6-14C aryl, 5-14C heteroaryl, 7-15C aralkyl, or 5-14C heteroaralkyl;
 Z3,Z4 = H or t1; or
 Y2+Y3 = -O(C(Z3)(Z4))rO-, -O(C(Z3)(Z4))r+1-, carbocycle or heterocycle.

Any CH3, CH2, or CH not attached to halo, SO, SO 2, N, O or S is optionally substituted by hydroxy, halo, (1-4C)alkyl, (1-4C)alkoxy or -di-(1-4C)alkyl-amino.

INDEPENDENT CLAIMS are also included for the following:

(1) a compound that modulates the activity of the CHK1 enzyme in vivo or in vitro (where the compound binds to at least one of Phe 93 and Asp 94 of the CHK1 enzyme in vivo and/or in vitro);

(2) a composition comprising (I) and an anti-neoplastic agent;

(3) preparation of (I); and

(4) treating a neoplasm or modulating the activity of a CHK1 enzyme comprising the administration of (I) where R1 may additionally be H.

ACTIVITY - Cytostatic; Antiinflammatory; Respiratory-Gen.; Antiallergic; Immunosuppressive; Antimicrobial; **Ophthalmological**; Cardiovascular-Gen.; CNS-Gen.; Hepatotropic; Nephrotropic; Gynecological; Gastrointestinal-Gen.; Dermatological; Antipsoriatic; Antiangiogenic; Vulnery; Antiulcer; Anti-HIV.

MECHANISM OF ACTION - CHK1 enzyme modulator; CDC25C binder inhibitor; Protein kinase (e.g. Checkpoint kinase 1 (CHK1), (CHK-2), Cyclin dependent kinase 1 (CDK1), Serum/glucocorticoid regulated kinase (SGK), Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK), Lymphoid T cell tyrosine kinase (LCK), Mitogen- and stress-activated protein kinase 1 (MSK1), Rho kinase (ROCK-II), P70S6 kinase (p70S6K), cAMP (adenosine 3',5'-cyclic monophosphate)-dependent protein kinase (PKA), Mitogen activated protein kinase (MAPK), (MAPK-1), (MAPK-2), Protein kinase C-related kinase 2 (PRK2), 3'-Phosphoinositide dependent kinase 1 (PDK1), Fyn kinase (FYN), Protein kinase C (PKC), (PKC- beta 2), (PKC gamma), Vascular endothelial growth factor receptor 2 (VEGFR-2), Fibroblast growth factor receptor (FGFR), Phosphorylase kinase (PHK), Wee1 kinase (Wee1), and Protein Kinase B (PKB)) receptor modulator or inhibitors. CHK1 Assay was carried out as follows: Production of ADP from ATP that accompanies phosphoryl transfer to the synthetic substrate peptide Syntide-2 (PLARTLSVAGLPGKK) was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) through the actions of pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored following the decrease of absorbance at 340 nm using a HP8452 spectrophotometer. Typical reaction solutions contained: PEP (4 mM); NADH (0.15 mM); LDH/ml (28 units); PK/ml (16 units); DTT (dithiothreitol) (3 mM); Syntide-2 (0.125 mM); ATP (0.15 mM); MgCl2 (25 mM) in Tris (50 mM), pH 7.5; and NaCl (400 mM) and 2-hydroxy-1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethyl 3,4-dichlorophenylcarbamate (IA) (test compound). Assay was initiated with FL-CHK1 (10 nM). The Ki value for (IA) was found to be less than 1 mu M.

USE - For modulating the CHK1 enzyme or the activity of protein kinase receptor; for the treatment of a disease by modulating the activity of CHK1 or by inhibiting the binding of CDC25C to CHK1 e.g. cancer; for the treatment of hyperproliferative disorder, e.g. cancer (e.g. brain, lung, kidney, renal, ovarian, ophthalmic, squamous cell, bladder, gastric, pancreatic, breast, head neck, oesophageal, gynecological, prostate, colorectal or thyroid cancers) or noncancerous disorders (e.g. benign hyperplasia of the skin or prostate), mammalian disease condition mediated by protein kinase activity associated with tumor growth, cell proliferation, or angiogenesis, or neoplasm (all claimed); connective tissue disorders, inflammatory disorders, immunology/allergy disorders, infectious diseases, respiratory diseases, cardiovascular diseases, eye diseases, metabolic diseases, central nervous system (CNS) disorders, liver/kidney diseases, reproductive health disorders, gastric disorders, skin disorders and cancers; psoriasis; eye diseases (e.g. aberrant angiogenesis, ocular angiogenesis, ocular inflammation, keratoconus, Sjogren's syndrome, myopia, ocular tumors, corneal graft rejection, corneal injury, nonvascular glaucoma, corneal ulceration, corneal scarring, macular degeneration (including age-related macular degeneration (including wet and dry forms)), proliferative vitreoretinopathy and retinopathy of prematurity). The cancer includes e.g. Ewing's tumor, Kaposi's sarcoma; uveal melanoma.

ADVANTAGE - (I) modulates the activity of the CHK1 enzyme in vivo and in vitro and the activity of protein kinase receptor. (I) selectively modulates the activity of CHK1 relative to other native kinases with a selectivity of at least 50-fold. (I) enhances the effect of DNA-damaging agents in a patient or the anti-neoplastic effect of radiation.

Dwg.0/1

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B05-B01E; B06-D05; B14-A01; B14-A02; B14-C03;
B14-D06C; B14-E10B; B14-F01; B14-F02; B14-F02F2;
B14-G02A; B14-G02C; B14-G02D; B14-G03; B14-H01;
B14-J01; B14-J05B; B14-K01; B14-N03;
B14-N07A; B14-N10; B14-N12; B14-N17; B14-P02;
B14-S13; B14-S16

TECH UPTX: 20050805

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation (Claimed): Preparation of (I) involves: contacting substituted 1H-benzimidazole compound of formula (III) with substituted isocyanato-benzene compound of formula (IV) in a solvent system under coupling conditions.

Preferred Compound: (I) has (1S) configuration at the CHR1 carbon atom.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: The anti-neoplastic agent is capable of damaging DNA in a malignant cell (preferably mitotic inhibitor, alkylating agent, anti-metabolite, intercalating antibiotic, enzyme, topoisomerase inhibitor, biological response modifier, anti-hormone, anti-androgen, and carrier).

ABEX UPTX: 20050805

SPECIFIC COMPOUNDS - 30 Compounds (I) are specifically claimed e.g. 2-hydroxy-1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethyl 3,4-dichlorophenylcarbamate of formula (IA).

ADMINISTRATION - (I) is administered in a dosage of 0.001 - 100 (preferably 1 - 35) mg/kg/day, in single or divided doses orally, intraduodenally, parenterally (including intravenously, subcutaneously, intramuscularly, intravascularly or by infusion), topically, rectally, pulmonarily (including by inhalation), intranasally or transdermally. For a 70 kg human, (I) is administered in a dosage of 0.05 - 7 (preferably 0.2 - 2.5) g/day.

EXAMPLE - A mixture of 3,4,5,6-tetramethyl-1,2-dinitrobenzene (5 g), Pd/C (0.9 g) and hydrazine (18 ml) in ethyl alcohol (200 ml) was refluxed for 2 hours. After filtration to remove the catalyst, the filtrate was concentrated to dryness. The residue (crude 1,2-diamino-3,4,5,6-tetramethylbenzene) was mixed with glyceric acid (25 g) in 1 N HCl solution. After work up, 1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethane-1,2-diol (A1) was obtained. To the solution of (A1) (0.50 g) in DMF (5 ml), was added imidazole (0.34 g) and tert-butyldimethylsilyl chloride (0.35 g). The reaction mixture was stirred at room temperature for 40 minutes. After work up, 2-((tert-butyl(dimethyl)silyl)oxy)-1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethanol (A2) was obtained. To the solution of (A2) (0.50 g) in toluene (25 ml), was added 3,4-dichlorophenylisocyanate (0.35 g). The mixture was stirred at 85degreesC for 2 hours. After work up, 2-((tert-butyl(dimethyl)silyl)oxy)-1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethyl 3,4-dichlorophenylcarbamate (A3) was obtained. To the solution of (A3) (0.70 g) in THF (20 ml), was added n-Bu4NF (2.6 ml). The mixture was stirred for 30 minutes. After work up, 2-hydroxy-1-(4,5,6,7-tetramethyl-1H-benzimidazol-2-yl)ethyl 3,4-dichlorophenylcarbamate (1A) was obtained (0.53 g; yield; 96%).

L640 ANSWER 42 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-371573 [38] WPIX
 DOC. NO. CPI: C2005-114914
 TITLE: New 2,6-disubstituted 7-oxo-pyrido(2,3-d)pyrimidine derivatives are p38-mitogen-activated protein kinase inhibitors, useful for the treatment of e.g. arthritis, irritable bowel syndrome and adult respiratory distress syndrome.
 DERWENT CLASS: B02
 INVENTOR(S): GOLDSTEIN, D M
 PATENT ASSIGNEE(S): (ROCH-N) ROCHE PALO ALTO LLC; (HOFF) HOFFMANN LA ROCHE & CO AG F
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
US 2005107408	A1	20050519	(200538)*		36	A61K031-519	
WO 2005047284	A1	20050526	(200538)	EN		C07D471-04	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2005107408	A1	Provisional	
		US 2003-519789P	20031113
		US 2004-987656	20041112
WO 2005047284	A1	WO 2004-EP12475	20041104

PRIORITY APPLN. INFO: US 2003-519789P 20031113; US
 2004-987656 20041112

INT. PATENT CLASSIF.:

MAIN: A61K031-519; C07D471-04
SECONDARY: A61P029-00; C07D487-02
INDEX: C07D471-04; C07D239:00; C07D221:00

BASIC ABSTRACT:

US2005107408 A UPAB: 20050616

NOVELTY - 2,6-Disubstituted 7-oxo-pyrido(2,3-d)pyrimidine derivatives (I) are new.

DETAILED DESCRIPTION - 2,6-Disubstituted 7-oxo-pyrido(2,3-d)pyrimidine derivatives of formula (I) are new.

X1 = O, S(O)n or C=O;

Ar1 = (hetero)aryl;

R1 = alkoxyalkyl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hydroxyalkyl or hydroxycycloalkyl;

R2 = hydroxyalkyl, oxoalkyl or hydroxycycloalkyl; and

n = 0-2.

ACTIVITY - Antiarthritic; Antiinflammatory; Gastrointestinal-Gen.; Respiratory-Gen.; Neuroprotective; Nootropic; Antipyretic; Antirheumatic; Osteopathic; Antipsoriatic; Antiasthmatic; Virucide; Antibacterial; Immunosuppressive; Antimalarial; Immunomodulator; Anti-HIV; Vasotropic; Cardiovascular-Gen.; Antiarteriosclerotic; Thrombolytic; Cardiant; Nephrotropic; Hepatotropic; CNS-Gen.; Cytostatic; Antidiabetic; Dermatological; Vulnerary; Antiulcer; **Ophthalmological**; Antiangiogenic; Endocrine-Gen.; Gynecological; Analgesic.

MECHANISM OF ACTION - P38-Mitogen-activated protein (MAP) kinase inhibitor.

Compounds (I) were tested for their p38-MAP kinase inhibitory activity using an in vitro assay. The results showed that the median inhibitory concentration of 6-(2,4-difluoro-phenoxy)-8-(3-hydroxy-propyl)-2-(tetrahydro-pyran-4-ylamino)-8H-pyrido(2,3-d)pyrimidin-7-one (Ib) was 0.0008 micro M.

USE - Compounds (I) are useful for the treatment of p38 mediated disorders (particularly arthritis, Crohn's disease, irritable bowel syndrome, adult respiratory distress syndrome, chronic obstructive pulmonary disease and Alzheimer's disease) (claimed). (I) are also useful for the treatment of fever, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, pulmonary disorders or lung inflammation (e.g. adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis and chronic pulmonary inflammatory disease), viral and bacterial infections (e.g. sepsis, septic shock, gram negative sepsis, malaria, meningitis or cachexia secondary to infection), cachexia secondary to AIDS, pneumonia, herpes virus, bone resorption diseases (e.g. endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft versus host reaction and allograft rejections), cardiovascular diseases/disorders (e.g. atherosclerosis, thrombosis, congestive heart failure and cardiac reperfusion injury), renal reperfusion injury, liver disease, nephritis, myalgias due to infection and central nervous system disorders.

Compounds (I) are also useful for the treatment of influenza, multiple sclerosis, cancer, diabetes, systemic lupus erythromatosis, skin-related conditions (e.g. psoriasis, eczema, burns and keloid formation), gastrointestinal conditions (e.g. inflammatory bowel disease, gastritis, irritable bowel syndrome and ulcerative colitis), **ophthalmic** diseases (e.g. retinopathies and uveitis), angiogenesis (e.g. neoplasia), **ophthalmological** conditions (e.g. corneal graft rejection and neovascular glaucoma), ulcerative diseases, diabetic nephropathy, cardiomyopathy, disorders of the female reproductive system (e.g. endometriosis), pain and hepatitis C virus. (I) are useful in veterinary treatment.

Dwg.0/0

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B06-D08; B14-A01; B14-A02; B14-A03B; B14-C01;
 B14-C03; B14-C04; B14-C06; B14-C09; B14-D06C;
 B14-E08; B14-E10; B14-E11B; B14-F01; B14-F02;
 B14-F04; B14-F05; B14-F07; B14-G02C; B14-G02D;
 B14-H01; B14-J01; B14-J05; B14-K01; B14-N01;
B14-N03; B14-N10; B14-N12; B14-N14; B14-N16;
 B14-N17; B14-P02; B14-S01; B14-S04; B14-S06; B14-S16
 TECH UPTX: 20050616

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Preparation of (I) comprises:

- (1) reaction of pyrimidine compounds of formula (1a) with a hydroxyalkyl amine (R2-NH2) in the presence of a solvent (e.g. dichloromethane) and a base (e.g. trialkyl amine) to give pyrimidine compounds of formula (1b);
- (2) reduction of (1b) in the presence of a solvent (e.g. lithium aluminum hydride) at room temperature to give alcohol compounds of formula (1c);
- (3) oxidation of (1c) with manganese dioxide in the presence of a solvent (e.g. dichloromethane) at 0 degrees C - 60 degrees C to give carboxaldehyde compounds of formula (1d);
- (4) reaction of (1d) with an ester (Ar1-X1CH2-CO2R1) in the presence of a base (e.g. potassium carbonate and sodium carbonate) to give pyrido(2,3-d)pyrimidin-7-one compounds of formula (1e);
- (5) oxidation of (1e) with an oxidizing agent (e.g. 3-chloroperbenzoic acid (MCPBA)) in the presence of a solvent (e.g. chloroform) to give pyrido(2,3-d)pyrimidin-7-one compound of formula (1f); and
- (6) reaction of (1f) with an amine (R1-NH2) in the presence or absence of solvent at 150 degrees C.

ABEX UPTX: 20050616

SPECIFIC COMPOUNDS - 48 compounds (I) are specifically claimed e.g. 6-(2,4-difluoro-phenoxy)-2-((R)-2-hydroxy-1-methyl-ethylamino)-8-((S)-2-hydroxy-propyl)-8H-pyrido(2,3-d)pyrimidin-7-one of formula (Ia).

ADMINISTRATION - Administration of (I) is 0.1-100 (preferably 0.5-5) mg/kg/day, orally, rectally or parenterally.

EXAMPLE - To a tetrahydrofuran (5 ml) solution of 6-(2,4-difluorophenoxy)-8-((S)-2-hydroxypropyl)-2-methanesulfonyl-8H-pyrido(2,3-d)pyrimidin-7-one (400 mg) was added (R)-2-amino-1-propanol (0.38 ml) and stirred overnight at room temperature. Concentrated under vacuum and the reaction mixture worked up to give 6-(2,4-difluoro-phenoxy)-2-((R)-2-hydroxy-1-methyl-ethylamino)-8-((S)-2-hydroxy-propyl)-8H-pyrido(2,3-d)pyrimidin-7-one (Ia) (370 mg).

DEFINITIONS - Preferred Definitions: In (I);

Ar1 = 2,4-disubstituted phenyl or 2,4-difluorophenyl;

X1 = O;

R1 = tetrahydropyranyl, 1-methyl-2-methoxyethyl, cyclopentyl, cyclopropyl, iso-propyl, cyclohexyl, 1-(2-hydroxyethyl)-3-hydroxypropyl, 1-hydroxymethyl-2-hydroxypropyl, 1-hydroxymethyl-3-hydroxypropyl, 1-methylpropyl, 2-hydroxy-1-methylethyl, 1-(2-methoxyethyl)-3-methoxypropyl, N-methanesulfonyl piperidinyl, ethyl, methyl, 2-hydroxypropyl, neopentyl, 1,1-dimethyl-2-hydroxyethyl, 1-(hydroxymethyl)propyl, 2-methylpropyl, cyclopropylmethyl, cyclobutyl, 1,2-dimethyl-2-hydroxypropyl, 1-(hydroxymethyl)-2-hydroxyethyl, (R)-2-hydroxy-1-methylethyl or (S)-2-hydroxy-1-methylethyl;

R2 = 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-(2-hydroxyethyl)-3-hydroxypropyl, 2-oxopropyl, (R)-2-hydroxypropyl or (S)-2-hydroxypropyl; and

n = 1-2.

L640 ANSWER 43 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2005-031046 [03] WPIX
 CROSS REFERENCE: 2004-034763 [03]; 2004-034766 [03]; 2004-420073 [39];
 2004-420074 [39]
 DOC. NO. CPI: C2005-009745
 TITLE: Use of immunomodulatory compound to treat, manage or
 prevent cancers e.g. advanced malignancy, amyloidosis,
 neuroblastoma, meningioma and hemangiopericytoma, and
 diseases associated with undesired angiogenesis.
 DERWENT CLASS: B02 B04 D16
 INVENTOR(S): ZELDIS, J B
 PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP
 COUNTRY COUNT: 108
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004103274	A2	20041202	(200503)*	EN	73	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004103274	A2	WO 2004-US14004	20040505

PRIORITY APPLN. INFO: US 2003-704237 20031106; US
 2003-438213 20030515

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2004103274 A UPAB: 20050112

NOVELTY - Treatment, management or prevention of a specific cancer or a disease associated with undesired angiogenesis, comprising administration of an immunomodulatory compound (A) or its salt, solvate or stereoisomer, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) treating, managing or preventing a specific cancer, comprising administering an immunomodulatory compound (A) or its salt, solvate or stereoisomer and a second active ingredient (B), radiation therapy, hormonal therapy, biological therapy or immunotherapy;

(2) treating, managing or preventing a disease associated with undesired angiogenesis, comprising administering an immunomodulatory compound (A) or its salt, solvate or stereoisomer and a second active ingredient (B);

(3) treating, preventing or managing a specific cancer, comprising administering (A) to a patient and transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient;

(4) a pharmaceutical composition comprising (A) or its salt, solvate or stereoisomer, and (B);

(5) a kit comprising a pharmaceutical composition comprising (A) and a pharmaceutical composition comprising (B); and

(6) a kit comprising a pharmaceutical composition comprising (A) and umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow.

ACTIVITY - Cytostatic; Neuroprotective; Endocrine-Gen.; Anti-HIV; Gynecological; Antiinflammatory; Cardiant; Nephrotropic; Antidiabetic; **Ophthalmological**; Immunosuppressive; **Keratolytic**; Antiseborrheic; Dermatological; Antibacterial; Antiulcer; Fungicide; Virucide; Protozoacide ; Antiarthritic; Antirheumatic; Tranquilizer; Vulnerary; Antiallergic; Vasotropic; Antianemic; Antisickling; Osteopathic; Cardiovascular-Gen.; CNS-Gen.; Gastrointestinal-Gen.; Cerebroprotective; Antiangiogenic.

MECHANISM OF ACTION - Tumor necrosis factor- alpha inhibitor.

USE - (A) is useful to treat/manage/prevent cancers (refractory to conventional therapies) such as advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant/relapsed/progressive brain tumor, malignant glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C and D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, metastatic/localized melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, multiple myeloma, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, leiomyoma, locally advanced bladder cancer, metastatic transitional cell bladder cancer, metastatic breast cancer, stage IIIB non-small cell lung cancer or multiple myeloma; and also to treat/manage/prevent a disease (endometriosis, Crohn's disease, heart failure, advanced heart failure, renal impairment, diabetic retinopathy, retinopathy of prematurity, **corneal** graft rejection, neovascular glaucoma, retrolental fibroplasia, proliferative vitreoretinopathy, trachoma, myopia, optic pits, epidemic **keratoconjunctivitis**, atopic **keratitis**, superior limbic **keratitis**, pterygium **keratitis** sicca, **Sjogren's**, acne rosacea, phlyctenulosis, syphilis, lipid degeneration, bacterial ulcer, fungal ulcer, Herpes simplex infection, Herpes zoster infection, protozoan infection, Mooren ulcer, Terrien's marginal degeneration, marginal **keratolysis**, rheumatoid arthritis, systemic lupus, polyarteritis, trauma, Wegener's sarcoidosis, scleritis, Steven's Johnson disease, periphigoid radial **keratotomy**, sickle cell anemia, sarcoid, pseudoxanthoma elasticum, Paget's disease, vein occlusion, artery occlusion, carotid obstructive disease, chronic uveitis, chronic vitritis, Lyme's disease, Eales disease, Bechet's disease, retinitis, choroiditis, presumed **ocular** histoplasmosis, Best's disease, Stargart's disease, pars planitis, chronic retinal detachment, hyperviscosity syndromes, toxoplasmosis, sclerosing cholangitis, rubeosis, endotoxemia, toxic shock syndrome, osteoarthritis, retrovirus replication, wasting, meningitis, silica-induced fibrosis, asbestos-induced fibrosis, veterinary disorder, malignancy-associated hypercalcemia, stroke, circulatory shock, periodontitis, gingivitis, macrocytic anemia, refractory anemia, or 5q-

syndrome) associated with undesired angiogenesis. (A) is also useful to avoid or reduce an adverse effect associated with the administration of (B), radiation therapy, hormonal therapy, biological therapy or immunotherapy in a patient suffering from a specific cancer (all claimed).

The ability of 3-(4-amino-1-oxo-1,3 -dihydro-isoindol-2-yl)-piperidine-2,6-dione (0.4 micro M) to treat cancer was assessed using multiple myeloma cell lines. The results showed that there was 50% inhibition of cell proliferation.

ADVANTAGE - The method is safe and effective to treat cancers. The method also reduces or avoids the toxicities and/or side effects associated with the conventional therapies.

Dwg.0/1

FILE SEGMENT: CPI
 FIELD AVAILABILITY: AB; GI; DCN
 MANUAL CODES: CPI: B01-A02; B01-B02; B02-C01; B02-D; B02-T; B03-A;
 B04-B03B; B04-G01; B04-G02; B04-G21; B04-H02B;
 B04-H04A; B04-H04C; B04-H05; B04-H06; B04-H07;
 B06-H; B07-D10; B08-C01; B10-B01A; B10-B03A;
 B14-A01; B14-A02A3; B14-A03; B14-A04; B14-C09;
 B14-D05C; B14-D06C; B14-E08; B14-E10C; B14-E11;
 B14-F01B; B14-F01E; B14-F02D1; B14-F02F2; B14-F03;
 B14-G02; B14-H01; B14-L01; B14-N03;
 B14-N06B; B14-N10; B14-N14; B14-N16; B14-N17;
 B14-S06; D05-H11A

TECH UPTX: 20050112

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: (A) is administered before, during or after surgery directed at relieving, reducing or avoiding a symptom of a specific cancer in the patient or (A) is administered prior to, during or after transplanting umbilical cord blood, placental blood, peripheral blood stem cell, hematopoietic stem cell preparation or bone marrow in the patient or administered prior to, during, or after the administration of (B), radiation therapy, hormonal therapy, biological therapy or immunotherapy.

Preferred Components: (A) is enantiomerically pure. (B) is anti-CD40 monoclonal antibody, histone deacetylase inhibitor, heat-shock protein-90 inhibitor, insulin-like growth factor-1 receptor kinase inhibitor, vascular endothelial growth factor receptor kinase inhibitor, inducer of apoptosis in multiple myeloma cell, statin, insulin growth factor receptor inhibitor, lysophosphatidic acid acyltransferase inhibitor, IκB kinase inhibitor, p38-mitogen activated protein kinase (MAPK) inhibitor, endothelial growth factor receptor (EGFR) inhibitor, human endothelial growth factor receptor (HER-2) antibody, vascular endothelial growth factor (VEGFR) antibody, VEGFR inhibitor, P13K inhibitor, C-Met inhibitor, monoclonal antibody, anti-TNF-alpha antibody, hematopoietic growth factor, cytokine, anti-cancer agent, antibiotic, cyclooxygenase-2 (Cox-2) inhibitor, immunomodulatory agent, immunosuppressive agent, corticosteroid, 2-methoxyestradiol, telomestatin, gefitinib, erlotinib hydrochloride, trastuzumab, pertuzumab, bevacizumab, wortmannin, rituximab, tositumomab, edrecolomab, semaxanib, cyclosporin, etanercept, doxycycline, bortezomib, oblimersen, melphalan, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), erythropoietin (EPO), topotecan, pentoxifylline, taxotere, irinotecan, ciprofloxacin, dexamethasone, doxorubicin, vincristine, interleukin-2 (IL-2), interferon, dacarbazine, Ara-C, vinorelbine, isotretinoin or a pharmacologically active mutant, salt, solvate and/or stereoisomer. (A) is a piperidine-2,6-dione compound of formulae (I) and (II).

X, Y = C=O or CH₂;

R = H or lower alkyl;

asterisk = chiral center;

R1 = H, 1-8C alkyl, 3-7C cycloalkyl, 2-8C alkenyl, 2-8C alkynyl, benzyl, aryl, 0-4C alkyl-(1-6C) heterocycloalkyl, 0-4C alkyl-(2-5C) heteroaryl, C(O)R3, C(S)R3, C(O)OR4, 1-8C alkyl-N(R6)2, (1-8C)alkyl-OR5, (1-8C)alkyl-C(O)OR5, C(O)NHR3, C(S)NHR3, C(O)NR3R3, C(S)NR3R3 or 1-8C alkyl-O(CO)R5;

R2 = H, F, benzyl, 1-8C alkyl, 2-8C alkenyl or 2-8C alkynyl;

R3 = 1-8C alkyl, 3-7C cycloalkyl, 2-8C alkenyl, 2-8C alkynyl, benzyl, aryl, 0-4C alkyl-(1-6C) heterocycloalkyl, (0-4C)alkyl-(2-5C) heteroaryl, (0-8C)alkyl-N(R6)2, (1-8C)alkyl-OR5, (1-8C)alkyl-C(O)OR5, (1-8C)alkyl-O(CO)R5 or C(O)OR5;

R4 = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, (1-4C)alkyl-OR5, benzyl, aryl, (0-4C)alkyl-(1-6C) heterocycloalkyl or (0-4C)alkyl-(2-5C) heteroaryl;

R5 = 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, benzyl, aryl or 2-5C heteroaryl;

R6 = H, 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, benzyl, aryl, 2-5C heteroaryl or (0-8C)alkyl-C(O)O-R5; or

two R6 = heterocycloalkyl; and

n = 0-1.

Provided that at least one of X and Y is C=O.

ABEX UPTX: 20050112

SPECIFIC COMPOUNDS - The use of 4-(amino)-2-(2,6-dioxo(3-piperidyl))-isoindoline-1,3-dione and 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione is specifically claimed as (A).

ADMINISTRATION - Administration of (A) is about 0.1-150 mg/day (claimed), orally in single or divided doses.

L640 ANSWER 44 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-833589 [82] WPIX

DOC. NO. CPI: C2004-289361

TITLE: Treating disease e.g., cystic fibrosis in human patient having mutation in cystic fibrosis transmembrane conductance regulator gene, involves administering peroxisome proliferator-activated receptor gamma inducer to patient.

DERWENT CLASS: B04 B05 D16

INVENTOR(S): FREEDMAN, S D

PATENT ASSIGNEE(S): (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT

COUNTRY COUNT: 108

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004098510	A2	20041118	(200482)*	EN	43	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE							
DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG							
KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ							
OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG							
US UZ VC VN YU ZA ZM ZW							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004098510	A2	WO 2004-US13412	20040430

PRIORITY APPLN. INFO: US 2003-466672P 20030430

INT. PATENT CLASSIF.:

MAIN: A61K000-00

BASIC ABSTRACT:

WO2004098510 A UPAB: 20041223

NOVELTY - Treating (M1) a disease in a human patient having a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, where the mutation is associated with the disease, involves administering peroxisome proliferator-activated receptor gamma (PPAR- gamma) inducer, PPAR- gamma agonist, AP-1 inhibitor, STAT inhibitor, nuclear factor kappa B (NFkappaB) inhibitor or an antioxidant to the patient.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for identifying (M2) a compound useful for treating a disease in a patient having a mutation in the CFTR gene, where the mutation is associated with the disease, involving:

(a) providing cells that express a PPAR gamma , contacting the cells with a candidate compound, and assessing the level of PPAR gamma expression in the cells relative to the level of PPAR gamma expression in the absence of the candidate compound, where the candidate compound that increases the level of PPAR gamma expression is identified as a compound useful for treating the disease;

(b) carrying out the providing and contacting steps as mentioned in (a), and assessing the half life of the PPAR gamma protein in the cells relative to the half life of the PPAR gamma protein in the absence of the candidate compound, where the candidate compound that increases the half life is identified as a compound useful for treating the disease; or

(c) carrying out the providing and contacting steps as mentioned in (a), and assessing the level of the PPAR gamma translocation to the nucleus of the cells relative to the level of PPAR gamma expression in the absence of the candidate compound, where the candidate compound that increases the level of PPAR gamma translocation to the nucleus is identified as a compound useful for treating the disease.

ACTIVITY - CNS-Gen.; Respiratory-Gen.; Antiinflammatory; Antiasthmatic; Antidiabetic.

MECHANISM OF ACTION - Inducer of PPAR- gamma ; PPAR- gamma agonist; AP-1 inhibitor; STAT inhibitor; NFkappaB inhibitor.

No supporting data is given.

USE - (M1) is useful for treating a disease in a human patient having a mutation in CFTR gene, where the mutation is associated with the disease chosen from cystic fibrosis, pancreatitis, chronic obstructive pulmonary disorder (COPD), asthma, chronic sinusitis, primary sclerosing cholangitis and congenital bilateral absence of the vas deferens (claimed). The PPAR gamma agonist is useful in the treatment of diabetes, and in decreasing inflammation.

DESCRIPTION OF DRAWING(S) - The figure is a bar graph representing peroxisome proliferator-activated receptor gamma mRNA expression levels in various tissues of cystic fibrosis transmembrane conductance regulator(-/-) and wild-type mice.

Dwg.1/7

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B03-A; B03-F; B03-H; B04-B03A; B04-C01A; B05-B01D; B05-B01P; B05-B02C; B05-C05; B06-A01; B06-D01; B06-D18; B07-B03; B07-D04C; B07-D12; B07-F01; B10-A06; B10-B01A; B10-B02D; B10-C03; B10-C04C; B10-C04E; B10-D03; B10-E02; B10-E03; B11-C07A; B11-C08; B12-K04E; B14-C03; B14-K01; B14-L01; B14-L06; B14-N04; B14-N13; B14-S03; B14-S04; B14-S08; D05-H09; D05-H17A6

TECH UPTX: 20041223

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M2), the cells

are pancreatic exocrine cells, lung cells, intestinal cells, bile duct cells, macrophages or their derivatives. The PPARgamma is PPARgamma1 or PPARgamma2. In (a) of (M2), the assessing step includes Western blotting. The assessing step involves measuring the amount of PPARgamma RNA in the cells. In (c) of (M2), the assessing step includes immunohistochemistry.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Components: In (M1), the PPAR-gamma is a PPAR-gamma1. The PPAR inducer is substantially pure eicosapentaenoic acid. The PPAR inducer is chosen from thiazolidinediones, fluoromethyloxycarbonyl, indomethacin, ibuprofen, fenoprofen and troglitazone. The PPAR ligand is rosiglitazone. The AP-1 inhibitor is chosen from nordihydroguaiaretic acid, SP600125, SR11302, pyrrolidine dithiocarbamate, curcumin, PD98059 and spiro compounds. The STAT inhibitor is chosen from SSI-1, SSI-2 and SSI-3. The STAT inhibitor is expressed in the target cell by gene therapy. The STAT inhibitor is a tripeptide having the sequence Pro-Tyr-Leu or Ala-Tyr-Leu, where the tyrosine is phosphorylated. The NFkappaB inhibitor is chosen from 2-chloro-N-(3,5-di(trifluoromethyl) phenyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide (SP-100030), 3,4-dihydro-4,4-dimethyl-2H-1,2-benzoselenazine (BXT-51072), declopramide (Oxi-104), dexlipotam, salicylanilide, 2-hydroxy-4-trifluoromethylbenzoic acid and 2-hydroxy-4-trifluoromethylbenzoic acid derivatives, where the 2-hydroxy-4-trifluoromethylbenzoic acid derivative is triflsal. The mutation is a deletion of Phe508. The antioxidant is a PPARgamma inducer. The antioxidant is chosen from Vitamin E, Vitamin C, S-adenosyl methionine, selenium, Vitamin C, beta-carotene, idebenone, cysteine, dithioerythritol, dithionite, dithiothreitol and pyrosulfite.

ABEX

UPTX: 20041223

ADMINISTRATION - The STAT inhibitor is administered by intravenous or inhalation route (claimed). A pharmaceutical composition comprising PPARgamma inducer and a carrier is administered by oral, intramuscular, intraperitoneal, subcutaneous, intrathecal or intracerebroventricular route, at a dosage of 0.1 microg/kg-100 mg/kg, preferably 250 microg/kg-5.0 mg/kg.

L640 ANSWER 45 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-561535 [54] WPIX
 DOC. NO. CPI: C2005-167552
 TITLE: Stent, useful to prevent or treat e.g. cardiovascular and renal diseases, comprises c-Jun N-terminal kinase inhibitor.
 DERWENT CLASS: A96 B02 B03 B07 D22
 INVENTOR(S): ZELDIS, J B
 PATENT ASSIGNEE(S): (CELG-N) CELGENE CORP; (ZELD-I) ZELDIS J B
 COUNTRY COUNT: 107
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2004060318	A2	20040722	(200454)*	EN	65	A61K000-00	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE							
LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP							
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG							
PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ							
VC VN YU ZA ZM ZW							
AU 2003300466	A1	20040729	(200477)			A61K000-00	
US 2005019366	A1	20050127	(200509)			A61K031-415	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004060318	A2	WO 2003-US41763	20031231
AU 2003300466	A1	AU 2003-300466	20031231
US 2005019366	A1 Provisional	US 2002-437332P	20021231
		US 2003-749344	20031230

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003300466	A1 Based on	WO 2004060318

PRIORITY APPLN. INFO: US 2003-749344 20031230; US
2002-437332P 20021231

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-415
SECONDARY: A61F002-00

BASIC ABSTRACT:

WO2004060318 A UPAB: 20050907

NOVELTY - Stent (I) comprising c-Jun N-terminal kinase inhibitor (A), is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a kit comprises (I) and directions for its use.

ACTIVITY - Cardiovascular-Gen.; Nephrotropic; Antiarteriosclerotic.

MECHANISM OF ACTION - c-Jun N-terminal kinase (JNK) inhibitor. (I) were assessed for JNK inhibitor activity in jurkat T cells. The median inhibitory concentration of (I) was 0.1-30 micro M.

USE - (I) are useful to prevent or treat cardiovascular or renal disease, atherosclerosis (claimed).

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: A12-V01; A12-V02; B04-C03B; B06-D05; B06-D18;
B06-E05; B06-F05; B07-D03; B07-D05; B07-D11;
B07-D12; B11-C04; B14-D06; B14-F01; B14-F02;
B14-F07; B14-N10; D09-C01

TECH UPTX: 20040823

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: (I) having coating comprises incorporated (A). (I) is indazole derivative of formula (a), pyrimidine-2-amine derivative of formula (b) or anthraquinone derivative of formula (c) and their salts, solvates or stereoisomers. (I) is a stent graft and it comprises polymer. The polymer is polyamide, a polyester, a polystyrene, a polypropylene, a polyacrylate, a polyvinyl, a polycarbonate, a polytetrafluorethylene, a polymethylmethacrylate, a polyethylene, a poly(ethylene terephthalate), a polyalkylene oxalate, a polyurethane, a polysiloxane, a poly(dimethyl siloxane), a polycyanoacrylate, a polyphosphazene, a poly(amino acid), a ethylene glycol dimethacrylate, a poly(methyl methacrylate), a poly(2-hydroxyethyl methacrylate), a poly (HEMA) or a polyhydroxyalkanoate. The coating is controlled-release coating. The method of (I) preparation further comprises surgical intervention. The intervention involves percutaneous coronary intervention, revascularisation, percutaneous transluminal coronary angioplasty, carotid percutaneous transluminal angioplasty coronary by-pass grafting, coronary angioplasty with stent implantation, renal angioplasty, peripheral percutaneous transluminal intervention of the iliac, femoral or popliteal arteries; or surgical intervention using impregnated artificial grafts. The implanting occurs prior, during or after to the administration of angioplasty.

A = bond, -(CH₂)a-, -(CH₂)bCH=CH(CH₂)c- or -(CH₂)bc =C(CH₂);
 R1 = (hetero)aryl or heterocycle fused to phenyl (all optionally substituted with 1-4 substituents of R3);
 R2 = R3, -R4, (CH₂)bC(O)R5, (CH₂)bC(O)OR5, (CH₂)bC(O)NR5R6, -(CH₂)bC(O)NR5(CH₂)CC(O)R6, (CH₂)bNR5C(O)R6, -(CH₂)bNR5C(O)NR6R7, -(CH₂)bNR5R6, -(CH₂)bOR5, -(CH₂)bSO2R5 or (CH₂)bSO2NR5R6;
 a = 1-6;
 b, c = 0-4;
 d = 0-2;
 R3 = halo, OH, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, substituted aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR8, -OC(O)R8, C(O)NR8R9, C(O)NR8OR9, SO2NR8R9, NR8SO2R9, CN, NO2, NR8R9, NR8C(O)R9, NR8C(O)(CH₂)OR9, NR8C(O)(CH₂)z,R9, -O(CH₂)bR8R9 or heterocycle fused to phenyl;
 R4 = alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (all optionally substituted with 1-4 substituents of R3 or R4 halo or OH);
 R5, R6, R7 = H, alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (optionally 1-4 substituents of R3); either
 R8, R9 = H, alkyl, aryl, arylalkyl, heterocycle, or heterocycloalkyl; or
 R8R9 = form a heterocycle (optionally substituted with 1-4 substituents of R3); and
 R0 = O, S, S(O), S(O)₂, NH or -CH₂.

Compound (c) being:

(a) unsubstituted;
 (b) monosubstituted and having a first substituent; or
 (c) disubstituted and having a first substituent and a second substituent; when first or second substituent present then it is at the 3-5, 7-10 position; first and second substituent, when present, are alkyl, hydroxy, halogen, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxy, aryl, aryloxy, arylalkoxy, arylalkyl, cycloalkylalkoxy, cycloalkoxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy or amine derivative of formula (1-6).

structures (1-6), page 62)

ABEX

UPTX: 20040823

SPECIFIC COMPOUNDS - The use of 34 compounds (A) is disclosed e.g. N-(6-oxo-6H-anthra(9,1-cd)isothiazol-5-yl)-benzamide, 7-dimethylamino-anthra(9,1-cd)isothiazol-6-one, 7-benzyloxy-2H-dibenzo(cd,g)indazol-6-one, (4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-phenyl)-(4-pyrrolidin-1-yl-piperidin-1-yl)-methanone, 1-(4-(4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-benzoyl)-piperazin-1-yl)-ethanone, 4-(4-(4-chloro-phenyl)-pyrimidin-2-ylamino)-N,N'-dimethyl-benzamide, 5-(5-(1,1-dimethyl-propyl)-1H-(1,2,4)triazol-3-yl)-3-(4-fluoro-phenyl)-1H-indazole and N-tert-butyl-3-(5-(1H-(1,2,4)triazol-3-yl)-1H-indazol-3-yl)-benzamide.

L640 ANSWER 46 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-374756 [35] WPIX
 DOC. NO. CPI: C2004-140905
 TITLE: Method for treating, preventing, managing and/or modifying pain involves use of c-Jun-N-terminal kinase inhibitor.
 DERWENT CLASS: B05
 INVENTOR(S): FALECK, H; MANNING, D C; ZELDIS, J B
 PATENT ASSIGNEE(S): (FALE-I) FALECK H; (MANN-I) MANNING D C; (ZELD-I) ZELDIS J B; (CELG-N) CELGENE CORP
 COUNTRY COUNT: 107
 PATENT INFORMATION:

PATENT NO KIND DATE WEEK LA PG MAIN IPC

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US 2004087642    A1 20040506 (200435)*      35 A61K031-416
WO 2004039325    A2 20040513 (200439)  EN      A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
    LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W:  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
    DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
    KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
    PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
    VC VN YU ZA ZM ZW
AU 2003284980    A1 20040525 (200468)      A61K031-416
EP 1553951       A2 20050720 (200547)  EN      A61K031-517
R:  AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV
    MC MK NL PT RO SE SI SK TR
BR 2003015573    A 20050830 (200558)      A61K031-517

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APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2004087642	A1 Provisional	US 2002-421104P	20021024
		US 2003-693793	20031023
WO 2004039325	A2	WO 2003-US34006	20031024
AU 2003284980	A1	AU 2003-284980	20031024
EP 1553951	A2	EP 2003-779300	20031024
		WO 2003-US34006	20031024
BR 2003015573	A	BR 2003-15573	20031024
		WO 2003-US34006	20031024

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003284980	A1 Based on	WO 2004039325
EP 1553951	A2 Based on	WO 2004039325
BR 2003015573	A Based on	WO 2004039325

PRIORITY APPLN. INFO: US 2002-421104P 20021024; US
2003-693793 20031023

INT. PATENT CLASSIF.:

MAIN: A61K000-00; A61K031-416; A61K031-517

SECONDARY: A61K031-415; A61K031-42; A61K031-425

BASIC ABSTRACT:

US2004087642 A UPAB: 20040603

NOVELTY - A method for treating, preventing, managing and/or modifying pain involves administration of c-Jun-N-terminal kinase (JNK) inhibitor, its salt, solvate or stereoisomer.

ACTIVITY - Analgesic; Virucide; Muscular-Gen.; Immunomodulator; Anticonvulsant; Neuroprotective; Antiinflammatory; Dermatological; Endocrine-Gen.; Osteopathic; Antidiabetic; Vulnerary; Antiarthritic; Antirheumatic; Cerebroprotective; Vasotropic.

MECHANISM OF ACTION - c-Jun-N-terminal Kinase (JNK) Inhibitor.

5-Amino-anthra(9,1-cd)isothiazol-6-one (A) was assayed for its inhibitory activity against p38-2 protein kinase according to the method described in Protein Phosphorylation, Sefton and Hunter, Eds., Academic Press, pp. 97-367, 1998. The IC50 value of (A) was found to be greater than 30000 nM.

USE - For treating, preventing, managing and/or modifying pain i.e. complex regional pain syndrome (preferably type I (having III stages) or type II) e.g. pain, autonomic dysfunction, trigeminal neuralgia,

post-herpetic neuralgia, cancer-related pain, phantom limb pain, fibromyalgia, chronic fatigue syndrome, radiculopathy, inability to initiate movement, weakness, tremor, muscle spasm, dytonia, dystrophy, atrophy, edema, stiffness, joint tenderness, increased sweating, sensitivity to temperature, light touch (allodynia), color change to the skin hyperthermic or hypothermic, increased nail and hair growth, early bony changes, hyperhidrotic with livedo reticularis or cyanosis, lost hair, ridged, cracked or brittle nails, dry hand, diffuse osteoporosis, irreversible tissue damage, thin and shiny skin, joint contractures, marked bone demineralization, diabetic neuropathy, luetic neuropathy, painful neuropathy induced iatrogenically by a drug or another painful neuropathic condition; nociceptive pain associated with a cut or contusion of the skin; a chemical or thermal burn; osteoarthritis; rheumatoid arthritis; or tendonitis; neuropathic pain associated with stroke, diabetic neuropathy, luetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, fibromyalgia, or painful neuropathy induced iatrogenically by a drug (all claimed).

ADVANTAGE - The method is safe and very effective.

Dwg.0/0

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B06-D05; B06-E05; B06-F05; B07-D12; B14-A02;
B14-C01; B14-C03; B14-C06; B14-C09; B14-D01;
B14-D06; B14-F02D; B14-G03; B14-J01B; B14-J07;
B14-N01; B14-N16; B14-N17; B14-S04

TECH UPTX: 20040603

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Compounds: The JNK inhibitor is a compound of formula (I) - (III).

A = direct bond, -(CH₂)_a-, -(CH₂)_bCH=CH(CH₂)_c- or -(CH₂)_bC_{triple}bondC(CH₂)_c-;

R₁ = (hetero)aryl or heterocycle fused to phenyl (all optionally mono- - tetra-substituted by R₃) (preferably phenylene (substituted by (R₃)₀₋₄));

R₂ = -R₃, R₄, -(CH₂)_bC(O)R₅-, -(CH₂)_bC(O)OR₅-, -(CH₂)_bC(O)NR₅R₆-, -(CH₂)_bC(O)NR₅(CH₂)_c-C(O)R₆-, -(CH₂)_bNR₅C(O)R₆-, -(CH₂)_bNR₅C(O)NR₆R₇-, -(CH₂)_bNR₅R₆-, -(CH₂)_bOR₅, (CH₂)_bSO_dR₅ or -(CH₂)_bSO₂NR₅R₆- (preferably -N(R₅)-C(O)-R₆);

a = 1 - 6;

b and c = 0 - 4;

d = 0 - 2;

R₃ = halo, hydroxy, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, optionally substituted aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR₈, -OC(O)R₈, -C(O)NR₈R₉, -C(O)NR₈OR₉, -SO₂NR₈R₉, -CN, -NO₂, -NR₈R₉, -NR₈C(O)R₉, -NR₈C(O)(CH₂)_bOR₉, -NR₈C(O)(CH₂)_bR₉, -O(CH₂)_bNR₈R₉ or heterocycle fused to phenyl;

R₄ = alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl (all optionally mono- - tetra-substituted by R₃), halo or hydroxy;

R₅ - R₉ = alkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl (all optionally mono- - tetra-substituted by R₃) or H;

R₈+R₉ = a heterocycle (all optionally mono- - tetra-substituted by R₃);

R'₁ = (hetero)aryl (optionally mono- - tetra-substituted by R₃)

(preferably phenyl (substituted at 4 position by R₇));

R'₂ = H;

R'₃ = H or lower alkyl (preferably H);

R'₄ = halo, hydroxy, lower alkyl, lower alkoxy or absent (preferably absent);

R'₅ and R'₆ = -R₈, -(CH₂)_rC(O)R'₉, -(CH₂)_rC(O)OR'₉, -(CH₂)_rC(O)NR'₉R₁₀, -(CH₂)_rC(O)NR'₉(CH₂)_tC(O)R₁₀, -(CH₂)_rNR'₉C(O)R₁₀, -(CH₂)_rNR₁₁C(O)NR'₉R₁₀, -(CH₂)_rNR'₉R₁₀, -(CH₂)_rOR'₉, -(CH₂)_rSO_cR'₉ or -(CH₂)_rSO₂NR'₉R₁₀;

NR'₅+R'₆ = optionally substituted heterocycle;

R'7 = halo, hydroxy, cyano, nitro, carboxy, alkoxy, (halo)alkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, aryl, arylalkyl, heterocycle, heterocycloalkyl, -C(O)OR'8, -OC(O)R'8, -C(O)NR'8R'9, -C(O)NR'8OR'9, -SOMR'8, -SOMNR'8R'9, -NR'8SOcR'9, -NR'8R'9, -NR'8C(O)R'9, -NR'9C(O)(CH2)TOR'9, -NR'8C(O)(CH2)TR'9, -O(CH2)tnRSR'9 or heterocycle fused to phenyl;
 R'8, R'9, R10 and R11 = H, optionally substituted alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl;
 R'8+R'9 = heterocycle;
 r and t = 0 - 4;
 m = 0 - 2;
 R' = -O-, -S-, -S(O)-, -S(O)2-, NH or -CH2-;
 R3+R4 = alkylidene or a heteroatom-containing cyclic alkylidene;
 R3 and R4 = H, (cyclo)alkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl or di-alkylaminoalkyl;
 R5 = H, (cyclo)alkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkyl, alkoxyalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl or di-alkylaminoalkyl.
 The compound of formula (III) is optionally mono or di-substituted at 3, 4, 5, 7, 8, 9, or 10 position by alkyl, hydroxy, halo, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxyalkyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, -N(R3)-R4, -NH-(alkyl)N(R3)-R4, -NH-C(O)-R5, -NH-S(O)2-R5, -C(O)-N(R4)-R3 or -S(O)2-N(R4)-R3.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method additionally involves administration of a second active agent.
 Preferred Components: The second active agent is an antidepressant, antihypertensive, anxiolytic, calcium channel blocker, muscle relaxant, non-narcotic analgesic, anti-inflammatory agent, cyclooxygenase-2 (COX-2) inhibitor, alpha-adrenergic receptor agonist or antagonist, ketamine, anesthetic, immunomodulatory agent, immunosuppressive agent, corticosteroid, hyperbaric oxygen, anticonvulsant, IMiD (RTM) and/or SelCID (RTM) (preferably gabapentin, thalidomide, salicyclic acid acetate, ketamine, celacoxib, carbamazepine, oxcarbazepine, phenytoin, sodium valproate, prednisone, nifedipine, clonidine, oxycodone, meperidine, morphine sulfate, hydromorphone, fentanyl, acetaminophen, ibuprofen, naproxen sodium, griseofulvin, amitriptyline, imipramine, doxepin, their salt, solvate or stereoisomer).

ABEX

UPTX: 20040603

SPECIFIC COMPOUNDS - 3-(4-Fluoro-phenyl)-5-(1H-(1,2,4)triazol-3-yl)-1H-indazole; and 5-amino-anthra(9,1-cd)isothiazol-6-one are specifically claimed as JNK inhibitor.

ADMINISTRATION - The dosage of JNK inhibitor is 0.001 - 1000 (preferably 0.001 - 500, especially 0.001 - 100 and particularly 0.001 - 1) mg/day and administered parenterally (e.g. intradermally, intramuscularly, intraperitoneally, intravenously or subcutaneously), epidurally or mucosally (e.g. intranasally, rectally, vaginally, sublingually, buccally or orally).

EXAMPLE - No relevant example given.

L640, ANSWER 47 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-833371 [77] WPIX

DOC. NO. CPI: C2003-234344

TITLE: Use of Jun N-terminal kinase inhibitor for treating

cancer.
 DERWENT CLASS: B02 B03
 INVENTOR(S): ENNIS, B W; STEIN, B M; WESTWICK, J K
 PATENT ASSIGNEE(S): (ENNI-I) ENNIS B W; (STEI-I) STEIN B M; (WEST-I) WESTWICK
 J K; (SIGN-N) SIGNAL PHARM INC
 COUNTRY COUNT: 103
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2003075917	A1	20030918	(200377)*	EN	109	A61K031-40	
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS							
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA							
ZM ZW							
US 2004067953	A1	20040408	(200426)			A61K038-00	
AU 2003217961	A1	20030922	(200431)			A61K031-40	
EP 1487436	A1	20041222	(200501)	EN		A61K031-40	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV							
MC MK NL PT RO SE SI SK TR							

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003075917	A1	WO 2003-US6894	20030307
US 2004067953	A1 Provisional	US 2002-362705P	20020308
		US 2003-384440	20030307
AU 2003217961	A1	AU 2003-217961	20030307
EP 1487436	A1	EP 2003-713937	20030307
		WO 2003-US6894	20030307

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2003217961	A1 Based on	WO 2003075917
EP 1487436	A1 Based on	WO 2003075917

PRIORITY APPLN. INFO: US 2003-384440 20030307; US
 2002-362705P 20020308

INT. PATENT CLASSIF.:

MAIN: A61K031-40; A61K038-00
 SECONDARY: A61K031-415; A61K031-42; A61K031-425; A61K031-505;
 A61K031-519; A61K031-525

BASIC ABSTRACT:

WO2003075917 A UPAB: 20031128

NOVELTY - Treatment, prevention or management of cancer involves administration of at least one Jun N-terminal kinase (JNK) inhibitor (A), and optionally another chemotherapeutic agent.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) reduction or prevention of at least one adverse effects or toxicities associated with the administration of chemotherapeutic agent or radiation therapy involving administration of at least one JNK inhibitor;

(2) increasing the efficacy of chemotherapeutic agent, for cancers resistant to treatment; reduces or prevents at least one adverse effects or toxicities associated with the administration of chemotherapeutic agent

or radiation therapy;

(3) reducing the dosage or frequency of administration of a chemotherapeutic agent or radiation therapy;

(4) increasing the anti-tumor activity of a chemotherapy agent or radiation therapy; and

(5) increasing the selective cytotoxicity of a chemotherapeutic agent.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Jun N-terminal kinase (JNK) inhibitor; Tumor growth inhibitor.

The tumor growth inhibitory efficiency of a combination of (3-(4-fluorophenyl)-5-(2H-(1,2,4)triazol-3-yl)-1H-indazole) and cyclophosphamide was evaluated in Lewis lung carcinoma model. Lewis lung carcinoma tumors were injected into C57BL/6 mice. Tumor were then treated by administration of vehicle (0.25 % Tween 80) (control), cyclophosphamide (50 mg/kg intraperitoneally) (test 1) and cyclophosphamide in combination with (3-(4-fluorophenyl)-5-(2H-(1,2,4)triazol-3-yl)-1H-indazole) (JNK inhibitor B) (test 2). Tumor volume (mm³) after 17 days were 1500/700/100 in control/test 1/test 2 respectively. The results showed that the JNK inhibitor B enhanced cytostatic efficacy of cyclophosphamide through an additive effect.

USE - For treating cancer (e.g. head, neck, eye, mouth, throat, esophagus, chest, bone, lung, colon, rectum, stomach, prostate, breast, ovaries, testicles or other reproductive organs, skin, thyroid, blood, lymph nodes, kidney, liver, pancreas, brain or central nervous system) in a patient (e.g. human) (claimed).

ADVANTAGE - The JNK inhibitor potentiate and synergize with, enhance the effectiveness of, improve the tolerance of, and/or reduce side effects caused by, other cancer therapies, biological therapies/immunotherapies, bone marrow transplants, stem cell replacement therapies and radiation therapies.

Dwg.0/6

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B04-G05; B05-A03B; B05-B01J; B06-H; B07-D12; B14-H01
TECH UPTX: 20031128

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The method further involves administration of chemotherapeutic agent.

Preferred Components: The chemotherapeutic agent is an apoptosis inducing agent, an anti-angiogenic agent, cytotoxic agent, an antimetabolite, an antimitotic agent, modulator of tumor necrosis factor (TNF)-alpha, tubulin stabilizing agent, a microtubule formation inhibiting agent, topoisomerase inhibitor, an anti-metastatic agent, DNA interactive agent (e.g. DNA alkylating agent or DNA intercalating agent) (preferably paclitaxel, irinotecan, phosphamide, 5-fluorouracil, cisplatin, carboplatin, methotrexate, doxorubicin, thalidomide, cetuximab, CC-4047 (RTM;) or CC-501 (RTM;)).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: The JNK inhibitor is a small organic molecule and is of formulae (I) - (III).
A = direct bond, -(CH₂)_a-, -(CH₂)_bCH=CH(CH₂)_c- or -(CH₂)_bC triple bond C(CH₂)_c-;

R1 = (hetero)aryl or heterocycle fused to phenyl (all optionally mono- to tetra-substituted by R3);

R2 = R3, R4, -(CH₂)_bC(O)R5, -(CH₂)_bC(O)OR5, -(CH₂)_bC(O)NR5R6, -(CH₂)_bC(O)NR5(CH₂)_cC(O)R6, -(CH₂)_bNR5C(O)R6, -(CH₂)_bNR5C(O)NR6R7, -(CH₂)_bNR5R6, -(CH₂)_bOR5, -(CH₂)_bSOdR5 or -(CH₂)_bSO2NR5R6;

a = 1 - 6;

b, c = 0 - 4;

d = 0 - 2;

R3 = aryl, arylalkyl, heterocycle, or heterocycloalkyl (all optionally

substituted), halo, OH, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, -C(O)OR8, -OC(O)R8, -C(O)NR8R9, -C(O)NR8OR9, -SO2NR8R9, -NR8SO2R9, -CN, -NO2, -NR8R9, -NR8C(O)R9, -NR8C(O)(CH2)bOR9, -NR8C(O)(CH2)bR9, -O(CH2)bNR8R9 or heterocycle fused to phenyl;

R4 = alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (all optionally mono- to tetra-substituted by R3), halo or OH;

R5 - R9 = alkyl, aryl, arylalkyl, heterocycle or heterocycloalkyl (all optionally mono- to tetra-substituted by R3) or H;

NR8R9 = heterocycle (all optionally mono- to tetra-substituted by R3);

R1a = (hetero)aryl optionally mono- to tetra-substituted by R7a;

R2a = H;

R3a = H or lower alkyl;

R4a = halo, OH, lower alkyl or lower alkoxy;

R5a, R6a = R8a, -(CH2)a1COR9a, -(CH2)a1C(O)OR9a, -(CH2)a1C(O)NR9aR10a, -(CH2)a1C(O)NR9a(CH2)b1C(O)R10a, -(CH2)a1NR9aC(O)R10a, -(CH2)a1NR11aC(O)NR9aR10a, -(CH2)a1OR9a, -(CH2)a1SOc1R9a or -(CH2)a1SO2NR9aR10a;

NR5aR6a = optionally substituted heterocycle;

R7a = optionally substituted aryl, arylalkyl, heterocycle, heterocycloalkyl (all optionally substituted), H, OH, CN, nitro, carboxy, alkyl, alkoxy, haloalkyl, acyloxy, thioalkyl, sulfinylalkyl, sulfonylalkyl, hydroxyalkyl, -C(O)OR8a, -OC(O)R8a, -C(O)NR8aR9a, -C(O)NR8aOR9a, -SOc1R8a, -SOc1NR8aR9a, NR8aSOc1R9a, -NR8aR9a, -NR8aC(O)R9a, -NR8aC(O)(CH2)b1OR9a, -NR8aC(O)(CH2)b1R9a, -O(CH2)b1NR8aR9a or heterocycle fused to phenyl;

R8a - R11a = alkyl, aryl, aralkyl, heterocycle, heterocycloalkyl (all optionally substituted) or H;

NR8aR9a = optionally substituted heterocycle;

a1, b1 = 0 - 4;

c1 = 0 - 2;

R0 = O, S, S(O), S(O)2, NH or CH2;

R3b+R4b = alkylidene or heteroatom-containing alkylidene;

R3b, R4b = H, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, aryloxyalkyl, alkoxyalkyl, aminoalkyl, mono-alkylaminoalkyl or di-alkylaminoalkyl; and

R5b = H, alkyl, cycloalkyl, aryl, arylalkyl, cycloalkylalkyl, alkoxy, alkoxyalkyl, alkoxyalkyl, alkoxyalkyl, amino, mono-alkylamino, di-alkylamino, arylamino, arylalkylamino, cycloalkylamino, cycloalkylalkylamino, aminoalkyl, mono-alkylaminoalkyl or di-alkylaminoalkyl.

R4a represents 1 - 4 substituents. (III) is optionally mono- or di-substituted. The first and the second substituent of (III) are at 3, 4, 5, 7, 8, 9 or 10 position and are selected from alkyl, OH, halo, nitro, trifluoromethyl, sulfonyl, carboxyl, alkoxyalkyl, alkoxy, aryl, aryloxy, arylalkyloxy, arylalkyl, cycloalkylalkyloxy, cycloalkyloxy, alkoxyalkyl, alkoxyalkoxy, aminoalkoxy, mono-alkylaminoalkoxy, di-alkylaminoalkoxy, -NR3bR4b, -NH-(alkyl)-NR3bR4b, -NH-C(O)R5b, -NH-SO2-R5b, -C(O)-NR3bR4b, or -SO2-NR3bR4b.

ABEX

UPTX: 20031128

SPECIFIC COMPOUNDS - 96 Compounds are specifically disclosed as JNK inhibitor, e.g. (3-(4-fluorophenyl)-5-(2H-(1,2,4)triazol-3-yl)-1H-indazole) (Ia).

ADMINISTRATION - The dosage of the JNK inhibitor is 0.001 - 3000 (preferably 0.001 - 750, especially 0.001 - 50, particularly 0.001 - 1) mg/day. The administration is parenteral (including intradermal, intramuscular, intraperitoneal, intravenous, or subcutaneous), epidural, mucosal (e.g. intranasal, rectal, vaginal, sublingual, buccal or oral), or by infusion or bolus injection.

EXAMPLE - No relevant example given.

L640 ANSWER 48 OF 79 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-040801 [03] WPIX
 DOC. NO. CPI: C2003-009781
 TITLE: Use of inhibitors of Jun Kinase (JNK) to treat metabolic disorders associated with insulin resistance, improve insulin sensitivity, diagnose insulin resistance, prevent obesity or inhibit fat accumulation in liver tissue.
 DERWENT CLASS: B02 B04
 INVENTOR(S): CHANG, L; HOTAMISLIGIL, G S; KARIN, M
 PATENT ASSIGNEE(S): (HARD) HARVARD COLLEGE; (REGC) UNIV CALIFORNIA
 COUNTRY COUNT: 101
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN	IPC
WO 2002085396	A1	20021031	(200303)*	EN	38	A61K035-78	
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ							
NL OA PT SD SE SL SZ TR TZ UG ZM ZW							
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK							
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR							
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT							
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM							
ZW							
EP 1390052	A1	20040225	(200415)	EN		A61K035-78	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT							
RO SE SI TR							
AU 2002307475	A1	20021105	(200433)			A61K035-78	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002085396	A1	WO 2002-US12687	20020424
EP 1390052	A1	EP 2002-764295	20020424
		WO 2002-US12687	20020424
AU 2002307475	A1	AU 2002-307475	20020424

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1390052	A1 Based on	WO 2002085396
AU 2002307475	A1 Based on	WO 2002085396

PRIORITY APPLN. INFO: US 2001-285966P 20010424
 INT. PATENT CLASSIF.:

MAIN: A61K035-78

BASIC ABSTRACT:

WO 200285396 A UPAB: 20030113

NOVELTY - Metabolic disorders associated with insulin resistance can be treated by the administration of an inhibitor of a NH2-terminal Jun Kinase (JNK).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) Method of improving insulin sensitivity by the administration of an inhibitor of JNK;

(2) Treating or preventing obesity by the administration of an inhibitor of JNK;

(3) Diagnosing insulin resistance or the risk of developing insulin

resistance by measuring the level of JNK activity or expression in a tissue, where an increase in activity or expression compared to normal indicates that the patient is suffering from or at risk of developing resistance; and

(4) Method of inhibiting fat accumulation in liver tissue by contacting the tissue with an inhibitor of JNK.

ACTIVITY - Antidiabetic; Anorectic; Hepatotropic; Dermatological; Virucide; Antiinfertility; Antiarteriosclerotic.

No biological data available.

MECHANISM OF ACTION - Inhibitor of JNK.

No biological data available.

USE - JNK is used for treating metabolic disorders associated with insulin resistance, improving insulin sensitivity, diagnosing insulin resistance, preventing or treating obesity or inhibiting fat accumulation in liver tissue (all claimed).

Also treating conditions associated with insulin resistance, e.g. cancer cachexia, HIV-1 infection, polycystic ovarian syndrome, atherosclerosis or severe burns.

DESCRIPTION OF DRAWING(S) - The figure shows bodyweight in JNK1-deficient mice compared to wild type control mice after both types of mouse were put on a high fat diet for 12 weeks.

Dwg.1/12

FILE SEGMENT: CPI

FIELD AVAILABILITY: AB; GI; DCN

MANUAL CODES: CPI: B02-H; B06-A01; B06-D06; B06-D09; B06-D18; B11-C08; B12-K04A; B14-A02B1; B14-D06; B14-E12; B14-F07; B14-J01A2; B14-N12; B14-N14; B14-N17A; B14-P02; B14-S04

TECH UPTX: 20030113

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: Inhibitor binds to an ATP binding site in JNK or to a catalytic domain of JNK. In inhibiting fat accumulation in liver tissue, the inhibitor preferentially reduces enzymatic activity of JNK1 compared to JNK2.

Preferred Inhibitor: The JNK is JNK1 or JNK2. The inhibitor is SP600125.

ABEX UPTX: 20030113

SPECIFIC COMPOUNDS - The JNK inhibitor is SP600125.

ADMINISTRATION - JNK is administered parenterally, enterally or topically in a dosage of 50-150 mug/kg.

EXAMPLE - Mice deficient in JNK1 or JNK2 were bred and placed on a high fat diet for 12 weeks. The group deficient in JNK1 had body weights of about 34 g compared with about 45 g for a control group. When fed on a standard diet, the body weights were about 28 and 26 g respectively.

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YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER, DRUGU, SCISEARCH' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 31 ANSWERS - CONTINUE? Y/(N):y

L640 ANSWER 49 OF 79 MEDLINE on STN DUPLICATE 4
 ACCESSION NUMBER: 2005098186 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15728539
 TITLE: Doxycycline inhibits TGF-beta1-induced MMP-9 via Smad and MAPK pathways in human corneal epithelial cells.
 AUTHOR: Kim Hyun-Seung; Luo Lihui; Pflugfelder Stephen C; Li De-Quan

CORPORATE SOURCE: Ocular Surface Center, Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, Houston, Texas, USA.

CONTRACT NUMBER: EY014553 (NEI)
EY11915 (NEI)

SOURCE: Investigative ophthalmology & visual science, (2005 Mar) 46 (3) 840-8.
Journal code: 7703701. ISSN: 0146-0404.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200504

ENTRY DATE: Entered STN: 20050301
Last Updated on STN: 20050414
Entered Medline: 20050413

ED Entered STN: 20050301
Last Updated on STN: 20050414
Entered Medline: 20050413

AB PURPOSE: To evaluate the effects of TGF-beta1 and doxycycline on production of gelatinase MMP-9 and activation of Smad, c-Jun N-terminal kinase (JNK), extracellular-regulated kinase (ERK), and p38 mitogen-activated protein kinase (MAPK) signaling pathways in human corneal epithelial cells. METHODS: Primary human corneal epithelial cells were cultured to confluence. The cells were treated with different concentrations of TGF-beta1 (0.1, 1, or 10 ng/mL), with or without TGF-beta1-neutralizing mAb (5 microg/mL), SP600125 (30 microM), PD98059 (40 microM), SB202190 (20 microM), or doxycycline (5-40 microg/mL) for different lengths of time. Conditioned media were collected from cultures treated for 24 to 48 hours to evaluate the MMP-9 production by zymography and activity assay. Total RNA was isolated from cells treated for 6 to 24 hours to evaluate MMP-9 expression by semiquantitative RT-PCR and Northern hybridization. Cells treated for 5 to 60 minutes were lysed in RIPA buffer for Western blot with phospho-specific antibodies against Smad2, JNK1/2, ERK1/2, or p38. RESULTS: TGF-beta1 increased expression, production, and activity of MMP-9 by human corneal epithelial cells in a concentration-dependent fashion. TGF-beta1 also induced activation of Smad2, JNK1/2, ERK1/2, and p38 within 5 to 15 minutes, with peak activation at 15 to 60 minutes. Doxycycline markedly inhibited the TGF-beta1-induced production of MMP-9 and activation of the Smad, JNK1/2, ERK1/2, and p38 signaling pathways. Its inhibitory effects were of a magnitude similar to SP600125, PD98059, and SB202190, specific inhibitors of the JNK1/2, ERK1/2, and p38 pathways, respectively. CONCLUSIONS: These findings demonstrated that doxycycline inhibits TGF-beta1-induced MMP-9 production and activity, perhaps through the Smad and MAPK signaling pathways. These inhibitory effects may explain the reported efficacy of doxycycline in treating MMP-9-mediated ocular surface diseases.

CT *Anti-Bacterial Agents: PD, pharmacology
Blotting, Northern
Blotting, Western
Cells, Cultured
*DNA-Binding Proteins: ME, metabolism
Dose-Response Relationship, Drug
*Doxycycline: PD, pharmacology
Epithelium, Corneal: CY, cytology
*Epithelium, Corneal: EN, enzymology
Extracellular Signal-Regulated MAP Kinases: ME, metabolism
*Gelatinase B: BI, biosynthesis

Gelatinase B: GE, genetics

Humans

JNK Mitogen-Activated Protein Kinases: ME, metabolism

*Mitogen-Activated Protein Kinases: ME, metabolism

RNA, Messenger: ME, metabolism

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Reverse Transcriptase Polymerase Chain Reaction

Signal Transduction

*Trans-Activators: ME, metabolism

*Transforming Growth Factor beta: AI, antagonists & inhibitors

Transforming Growth Factor beta: PD, pharmacology

p38 Mitogen-Activated Protein Kinases: ME, metabolism

RN 564-25-0 (Doxycycline)

CN 0 (Anti-Bacterial Agents); 0 (DNA-Binding Proteins); 0 (RNA, Messenger); 0 (Smad2 protein); 0 (Trans-Activators); 0 (Transforming Growth Factor beta); 0 (transforming growth factor beta1); EC 2.7.1.37 (Extracellular Signal-Regulated MAP Kinases); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases); EC 3.4.24.35 (Gelatinase B)

L640 ANSWER 50 OF 79

MEDLINE on STN

DUPLICATE 5

ACCESSION NUMBER: 2005366643 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15825184

TITLE: Areca (betel) nut extract activates mitogen-activated protein kinases and NF-kappaB in oral keratinocytes.

AUTHOR: Lin Shu-Chun; Lu Suu-Yi; Lee Szu-Ying; Lin Chi-Yen; Chen Chun-Hsien; Chang Kuo-Wei

CORPORATE SOURCE: Institute of Oral Biology, School of Dentistry, National Yang-Ming University, Peitou, Taipei, Taiwan.

SOURCE: International journal of cancer. Journal international du cancer, (2005 Sep 10) 116 (4) 526-35.
Journal code: 0042124. ISSN: 0020-7136.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200508

ENTRY DATE: Entered STN: 20050719

Last Updated on STN: 20050825

Entered Medline: 20050824

ED Entered STN: 20050719

Last Updated on STN: 20050825

Entered Medline: 20050824

AB Areca (betel) was recently proved a carcinogenic substance by the International Agency for Research on Cancer. However, the signaling impact of areca in oral keratinocyte is still obscure. Mitogen-activated protein kinase superfamilies, including extracellular signal-regulated kinase (ERK), **c-Jun N-terminal kinases** (JNK) and p38, together with transcription factor NF-kappaB, are important signaling elements. We examined the activation of these signaling pathways in OECM-1 and SAS oral keratinocytes, treated with ripe areca nut extract (ANE). In both cells, a rapid increase in **JNK1** activity at 0.5 hr was noted following treatment of ANE. ERK was profoundly activated during 0.5-2 hr in OECM-1 cells. Contrasting p38 activity was noted in these 2 cells. In both cells, ANE also activated NF-kappaB pathway in a biphasic manner, particularly for SAS cells. NF-kappaB was activated by approximately 2- to 4-fold at 0.5-1 hr and a plateau or slight decrease of activity existed between 1 and 6 hr. Later, another higher episode of NF-kappaB activity was raised. This was

accompanied with the rapid degradation in cytosolic IkappaBalpha as well as an increase of nuclear NF-kappaB in both cells. ANE treatment did not activate epidermal growth factor receptor signaling system, but blockage of NF-kappaB activation rendered the suppression of ANE-modulated COX-2 upregulation in OECM-1. This study identified that ANE affected interactive signaling systems in oral keratinocytes that could be the pathogenetic basis for areca.

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CT *Areca: CH, chemistry
 Carcinoma, Squamous Cell: ET, etiology
 Cell Culture Techniques
 Cell Transformation, Neoplastic
 Enzyme Activation
 Humans
 Keratinocytes
 *Mitogen-Activated Protein Kinase 8: ME, metabolism
 Mouth: CY, cytology
 Mouth Neoplasms: ET, etiology
 *NF-kappa B: PH, physiology
 *Plant Extracts: PD, pharmacology
 Plant Extracts: TO, toxicity
 Research Support, Non-U.S. Gov't
 Signal Transduction
 *p38 Mitogen-Activated Protein Kinases: ME, metabolism
 CN 0 (NF-kappa B); 0 (Plant Extracts); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 8); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases)

L640 ANSWER 51 OF 79 MEDLINE on STN DUPLICATE 7
 ACCESSION NUMBER: 2004584561 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15557436
 TITLE: Stimulation of matrix metalloproteinases by hyperosmolarity via a JNK pathway in human corneal epithelial cells.
 AUTHOR: Li De-Quan; Chen Zhuo; Song Xiu Jun; Luo Lihui; Pflugfelder Stephen C
 CORPORATE SOURCE: Ocular Surface Center, Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, 6565 Fannin Street, Houston, TX 77030, USA.
 CONTRACT NUMBER: EY014553 (NEI)
 EY11915 (NEI)
 SOURCE: Investigative ophthalmology & visual science, (2004 Dec) 45 (12) 4302-11.
 Journal code: 7703701. ISSN: 0146-0404.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200501
 ENTRY DATE: Entered STN: 20041124
 Last Updated on STN: 20050104
 Entered Medline: 20050103
 ED Entered STN: 20041124
 Last Updated on STN: 20050104
 Entered Medline: 20050103
 AB PURPOSE: To investigate whether exposure of human corneal epithelial cells to hyperosmotic stress activates the c-Jun NH(2)-terminal kinase (JNK) stress-activated protein kinase (SAPK) pathway, and stimulates production of the matrix metalloproteinases (MMPs): gelatinase (MMP-9), collagenases (MMP-1 and -13), and stromelysin (MMP-3). METHODS:

Primary human **corneal** epithelial cells cultured in normal osmolar medium (312 mOsM) were exposed to media with higher osmolarity (350-500 mOsM) achieved by adding NaCl, with or without SB202190, an inhibitor of the JNK pathway; dexamethasone; or doxycycline for different lengths of time. The conditioned media were collected after 24 hours of exposure for zymography and ELISA. Total RNA was extracted from cultures treated for 6 hours and subjected to semiquantitative RT-PCR. Cells treated for 5 to 60 minutes were lysed in RIPA buffer and subjected to Western blot with phospho (p)-specific antibodies against p-JNK and p-c-Jun. **JNK1** activation was also detected with an immunoassay system. RESULTS: The concentrations of MMP-9, -1, and -3 proteins in 24-hour conditioned media of **corneal** epithelial cells progressively increased as the media's osmolarity was increased from 312 to 500 mOsM by the addition of NaCl. The concentration of MMP-13 progressively increased to a peak at 450 mOsM. Active p-JNK-1, p-JNK-2, and p-c-Jun were detected by Western blot as early as 5 minutes and peaked at 60 minutes in cells exposed to hyperosmolar media. The levels of p-JNK-1, p-JNK-2, and p-c-Jun correlated positively with the osmolarity of the culture media. The p-JNK inhibitor SB202190 and doxycycline markedly inhibited the stimulation of p-JNK-1, p-JNK-2, and p-c-Jun, as well as MMP-9, -1, -13, and -3 at both the mRNA and protein levels in the cells exposed to hyperosmolar media. CONCLUSIONS: Expression and production of MMP-9, -1, -13, and -3 by human **corneal** epithelial cells correlated positively with increasing media osmolarity. This increase was mediated at least in part through activation of the JNK SAPK pathway. Doxycycline, an agent used to treat MMP-mediated **ocular** surface disease, inhibited the hyperosmolarity-induced MMP production and JNK activation. The relevance of these findings to stimulated production of MMPs by the elevated **tear** osmolarity in dry **eye** remains to be determined.

CT Adolescent
Adult
Anti-Inflammatory Agents: PD, pharmacology
Cells, Cultured
Doxycycline: PD, pharmacology
Enzyme Activation: DE, drug effects
Enzyme Inhibitors: PD, pharmacology
Epithelium, Corneal: CY, cytology
Epithelium, Corneal: DE, drug effects
*Epithelium, Corneal: EN, enzymology
Humans
Imidazoles: PD, pharmacology
JNK Mitogen-Activated Protein Kinases: AI, antagonists & inhibitors
*JNK Mitogen-Activated Protein Kinases: ME, metabolism
*MAP Kinase Signaling System: PH, physiology
Matrix Metalloproteinases: AI, antagonists & inhibitors
Matrix Metalloproteinases: BI, biosynthesis
*Matrix Metalloproteinases: ME, metabolism
Middle Aged
Osmolar Concentration
Pyridines: PD, pharmacology
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
RN 564-25-0 (Doxycycline)
CN 0 (4-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)imidazole); 0 (Anti-Inflammatory Agents); 0 (Enzyme Inhibitors); 0 (Imidazoles); 0 (MAP Kinase Signaling System); 0 (Pyridines); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 3.4.24.- (Matrix Metalloproteinases)

L640, ANSWER 52 OF 79 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2004584560 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15557435
TITLE: Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface.
AUTHOR: Luo Lihui; Li De-Quan; Doshi Amish; Farley William; Corrales Rosa M; Pflugfelder Stephen C
CORPORATE SOURCE: Ocular Surface Center, Cullen Eye Institute, Department of Ophthalmology, Baylor College of Medicine, 6565 Fannin Street, Houston, TX 77030, USA.
CONTRACT NUMBER: EY11915 (NEI)
SOURCE: Investigative ophthalmology & visual science, (2004 Dec) 45 (12) 4293-301.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 20041124
Last Updated on STN: 20050104
Entered Medline: 20050103
ED Entered STN: 20041124
Last Updated on STN: 20050104
Entered Medline: 20050103
AB PURPOSE: To evaluate whether experimentally induced dry eye in mice activates mitogen-activated protein kinase (MAPK) signaling pathways, c-Jun N-terminal kinases (JNK), extracellular-regulated kinases (ERK), and p38 and stimulates ocular surface inflammation. METHODS: 129SvEv/CD-1 mixed mice aged 6 to 8 weeks were treated with systemic scopolamine and exposure to an air draft for different lengths of time, from 4 hours to 10 days. Untreated mice were used as the control. The concentrations of IL-1beta and TNF-alpha in tear fluid washings and in corneal and conjunctival epithelia were measured by ELISA. MMP-9 in tear washings was evaluated by zymography, and gelatinase activity in the cornea and conjunctiva was determined by in situ zymography. Corneal and conjunctival epithelia were lysed in RIPA buffer for Western blot with MAPK antibodies, or they were lysed in 4 M guanidium thiocyanate solution for extraction of total RNA, which was used to determine gene expression by semiquantitative RT-PCR, real-time PCR, and gene array. RESULTS: Compared with those in age-matched control subjects, the concentrations of IL-1beta and MMP-9 in tear fluid washings and the concentrations of IL-1beta and TNF-alpha and gelatinolytic activity in the corneal and conjunctival epithelia were significantly increased in mice receiving treatments to induce dry eye after 5 or 10 days. The expression of IL-1beta, TNF-alpha, and MMP-9 mRNA by the corneal and conjunctival epithelia was also stimulated in mice treated for 5 or 10 days. The levels of phosphorylated JNK1/2, ERK1/2, and p38 MAPKs in the corneal and conjunctival epithelia were markedly increased as early as 4 hours after treatment, and they remained elevated up to 5 days. CONCLUSIONS: Experimental dry eye stimulates expression and production of IL-1beta, TNF-alpha, and MMP-9 and activates MAPK signaling pathways on the ocular surface. MAPKs are known to stimulate the production of inflammatory cytokines and MMPs, and they could play an important role in the induction of these factors that have been implicated in the pathogenesis of dry eye disease.

CT Animals

Conjunctiva: ME, metabolism
 Cytokines: BI, biosynthesis
***Dry Eye Syndromes: ME, metabolism**
 Enzyme-Linked Immunosorbent Assay
 Epithelium: ME, metabolism
Epithelium, Corneal: ME, metabolism
***Eye: ME, metabolism**
 *Gelatinase B: BI, biosynthesis
 Gelatinase B: GE, genetics
 Inflammation Mediators: ME, metabolism
 *Interleukin-1: BI, biosynthesis
 Interleukin-1: GE, genetics
 *MAP Kinase Signaling System: PH, physiology
 Mice
 Mice, Inbred Strains
 Osmolar Concentration
 RNA, Messenger: ME, metabolism
 Research Support, Non-U.S. Gov't
 Research Support, U.S. Gov't, P.H.S.
 Reverse Transcriptase Polymerase Chain Reaction
Tears: ME, metabolism
 Time Factors
 *Tumor Necrosis Factor-alpha: BI, biosynthesis
 Tumor Necrosis Factor-alpha: GE, genetics

CN 0 (Cytokines); 0 (Inflammation Mediators); 0 (Interleukin-1); 0 (MAP Kinase Signaling System); 0 (RNA, Messenger); 0 (Tumor Necrosis Factor-alpha); EC 3.4.24.35 (Gelatinase B)

L640 ANSWER 53 OF 79 MEDLINE on STN DUPLICATE 9
 ACCESSION NUMBER: 2004419296 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15326113
 TITLE: Dexamethasone inhibition of IL-1-induced collagen degradation by **corneal** fibroblasts in three-dimensional culture.
 AUTHOR: Lu Ying; Fukuda Ken; Liu Yang; Kumagai Naoki; Nishida Teruo
 CORPORATE SOURCE: Department of Biomolecular Recognition and Ophthalmology, Yamaguchi University School of Medicine, Japan.
 SOURCE: Investigative ophthalmology & visual science, (2004 Sep) 45 (9) 2998-3004.
 Journal code: 7703701. ISSN: 0146-0404.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200410
 ENTRY DATE: Entered STN: 20040825
 Last Updated on STN: 20041008
 Entered Medline: 20041007

ED Entered STN: 20040825
 Last Updated on STN: 20041008
 Entered Medline: 20041007

AB PURPOSE: Corticosteroids regulate the functions of inflammatory cells. The purpose of the present study was to investigate the effect of dexamethasone on collagen degradation by **corneal** fibroblasts, an underlying cause of **corneal** ulceration. METHODS: Rabbit **corneal** fibroblasts were cultured in three-dimensional gels of type I collagen and in the absence or presence of IL-1beta or dexamethasone. The extent of collagen degradation was determined by measurement of the amount of hydroxyproline generated by acid-heat

hydrolysis of culture supernatants. The expression of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) was evaluated by immunoblot analysis, gelatin zymography, and reverse transcription and real-time polymerase chain reaction. The phosphorylation of mitogen-activated protein kinases (MAPKs) in **corneal** fibroblasts was assessed by immunoblot analysis. **RESULTS:** Dexamethasone inhibited IL-1beta-induced collagen degradation by **corneal** fibroblasts in a dose-dependent manner. Both the synthesis and activation of MMPs and the expression of TIMPs were inhibited by dexamethasone, as was the activity of plasmin in culture supernatants. Dexamethasone also inhibited the IL-1beta-induced phosphorylation of the MAPKs extracellular signal-regulated kinase (ERK) and **c-Jun N-terminal kinase (JNK)**, but not that of p38. **CONCLUSIONS:** Dexamethasone exerted multiple effects on the MMP-TIMP system in **corneal** fibroblasts and thereby inhibited IL-1beta-induced collagen degradation by these cells. Inhibition of the IL-1beta-induced activation of ERK and JNK may contribute to these effects of dexamethasone.

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CT Check Tags: Male

Animals

*Anti-Inflammatory Agents: PD, pharmacology
Cells, Cultured

*Collagen: AI, antagonists & inhibitors

Collagen: ME, metabolism

Cornea: CY, cytology

Cornea: DE, drug effects

*Cornea: ME, metabolism

Cytological Techniques

*Dexamethasone: PD, pharmacology

*Fibroblasts: ME, metabolism

*Interleukin-1: PD, pharmacology

Matrix Metalloproteinases: BI, biosynthesis

Matrix Metalloproteinases: ME, metabolism

Mitogen-Activated Protein Kinases: ME, metabolism

Phosphorylation: DE, drug effects

Plasmin: ME, metabolism

Rabbits

Research Support, Non-U.S. Gov't

Tissue Inhibitor of Metalloproteinases: ME, metabolism

RN 50-02-2 (Dexamethasone); 9007-34-5 (Collagen)

CN 0 (Anti-Inflammatory Agents); 0 (Interleukin-1); 0 (Tissue Inhibitor of Metalloproteinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 3.4.21.7 (Plasmin); EC 3.4.24.- (Matrix Metalloproteinases)

L640 ANSWER 54-OF 79

MEDLINE on STN

DUPLICATE 14

ACCESSION NUMBER: 2003560610 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14638727

TITLE: Expression and activity of the signaling molecules for mitogen-activated protein kinase pathways in human, bovine, and rat lenses.

AUTHOR: Li David Wan-Cheng; Liu Jin-Ping; Wang Juan; Mao Ying-Wei; Hou Li-Hui

CORPORATE SOURCE: Hormel Institute, University of Minnesota, 801 16th Avenue NE, Austin, MN 55912, USA.. dwcli@hi.umn.edu

CONTRACT NUMBER: EY 11372 (NEI)

SOURCE: Investigative ophthalmology & visual science, (2003 Dec) 44. (12) 5277-86.

Journal code: 7703701. ISSN: 0146-0404.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200312
 ENTRY DATE: Entered STN: 20031202
 Last Updated on STN: 20031219
 Entered Medline: 20031209

ED Entered STN: 20031202
 Last Updated on STN: 20031219
 Entered Medline: 20031209

AB PURPOSE: The mitogen-activated protein kinase (MAPK) pathways play distinct roles in the lens. However, the expression patterns and activity levels of various components for these pathways have not been well-documented in vertebrate lenses, especially human lens. In the present study, the expressions and activities of extracellular signal-regulated kinase (ERK)-1/2/3, c-Jun NH2-terminal kinase (JNK)-1/2, p38 kinase, mitogen-activated protein kinase kinase (MEK)-1/2, and RAF1 were recorded in human, bovine, and rat lenses. METHODS: Human, bovine, and rat lenses were isolated from intact eyes. The epithelia and different layers of fiber cells were isolated from these lenses. Total proteins extracted from these samples were subject to analysis of the expression patterns and activity levels of the MAPKs and the activating kinases of ERK1/2. RESULTS: ERK1 and ERK2 were the most abundant MAPKs in terms of both protein and activity levels in all lenses. JNK1 and JNK2 were highly expressed in bovine lens, which differed from the pattern shared by human and rat lenses. p38 kinase was similarly expressed in bovine and rat lenses, but different from that in human lens. However, p38 kinase activity was exclusively detected in the epithelia. All lenses had MEK1/2 activity in their epithelia but the expression patterns of MEK1 and MEK2 differed in these lenses. RAF1 was expressed in the epithelia of all lenses, but its activity was detected only in rat lens. CONCLUSIONS: ERK1 and ERK2 are the most abundant MAPKs in the ocular lens, providing the basis for their multiple functions in lens development and pathogenesis. The dominant epithelial distribution of JNK1/2 and p38 kinase suggests that the lens epithelium is a major site for stress response. ERK1, p38 kinase, and PKCalpha can be used as molecular markers for aging.

CT Check Tags: Comparative Study
 Aged
 Aged, 80 and over
 Animals
 Cattle
 Epithelial Cells: EN, enzymology
 Humans
 *Lens, Crystalline: EN, enzymology
 MAP Kinase Kinase 1
 MAP Kinase Kinase 2
 *MAP Kinase Signaling System: PH, physiology
 Middle Aged
 Mitogen-Activated Protein Kinase 1: ME, metabolism
 Mitogen-Activated Protein Kinase 3
 Mitogen-Activated Protein Kinase 8
 Mitogen-Activated Protein Kinase 9
 Mitogen-Activated Protein Kinases: ME, metabolism
 *Mitogen-Activated Protein Kinases: ME, metabolism
 Protein-Serine-Threonine Kinases: ME, metabolism
 Protein-Tyrosine Kinase: ME, metabolism
 Proto-Oncogene Proteins c-raf: ME, metabolism
 Rats
 Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.
p38 Mitogen-Activated Protein Kinases

CN 0 (MAP Kinase Signaling System); EC 2.7.1.- (MAP Kinase Kinase 1); EC 2.7.1.- (MAP Kinase Kinase 2); EC 2.7.1.- (MAP2K1 protein, human); EC 2.7.1.- (MAP2K2 protein, human); EC 2.7.1.- (Mitogen-Activated Protein Kinase Kinases); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 1); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 3); EC 2.7.1.37 (**Mitogen-Activated Protein Kinase 8**); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 9); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Protein-Serine-Threonine Kinases); EC 2.7.1.37 (Proto-Oncogene Proteins c-raf); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases)

L640 ANSWER 55 OF 79 MEDLINE on STN DUPLICATE 15
 ACCESSION NUMBER: 2003095868 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 12601065
 TITLE: Activation and role of MAP kinase-dependent pathways in retinal pigment epithelium cells: **JNK1**, P38 kinase, and cell death.
 AUTHOR: Hecquet Christiane; Lefevre Gaelle; Valtink Monika; Engelmann Katrin; Mascarelli Frederic
 CORPORATE SOURCE: Cordeliers Biomedical Institute, National Institute of Health and Medical Research, Unit 450, National Center for Scientific Research, Paris, France.
 SOURCE: Investigative ophthalmology & visual science, (2003 Mar) 44 (3) 1320-9.
 Journal code: 7703701. ISSN: 0146-0404.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200303
 ENTRY DATE: Entered STN: 20030302
 Last Updated on STN: 20030311
 Entered Medline: 20030310
 ED Entered STN: 20030302
 Last Updated on STN: 20030311
 Entered Medline: 20030310
 AB PURPOSE: Retinal pigment epithelial (RPE) cell death is an important step in the pathogenesis of **ocular** diseases. **JNK1** and P38 kinase, two stress-activated kinases, play key roles relaying stress signals leading to cell death through cyclin D1 and c-Myc. Recently, stress-activated kinases have been shown to regulate cell proliferation. In the current study, the involvement of the **JNK1** and P38 kinase signaling pathways in RPE cell proliferation and death was investigated. METHODS: RPE cell proliferation was stimulated with 10% fetal calf serum (FCS). Activation of the **JNK1** and P38 kinase cascades and their potential targets was detected by Western blot analysis. Pharmacologic inhibitors and activators, and antisense oligodeoxynucleotides (ODN) directed against the stress kinases were used to analyze the signaling involved in RPE cell death. RESULTS: P38 and **JNK1** and their respective upstream activating kinases, MKK3/6 and -4, were all transiently activated in FCS-stimulated RPE cell cultures. Ras controlled only the activation of **JNK1**, whereas Rho transmitted the activation of both **JNK1** and P38, suggesting parallel signaling pathways and cross talk between the two kinases. Pharmacologic inhibition of **JNK1** did not affect cell proliferation in FCS-stimulated cells. Inactivation of P38 kinase and antisense ODN-induced downregulation of P38 kinase also had no effect on cell proliferation.

Long-term, high-level activation of **JNK1** and P38 kinase occurred during serum depletion-induced RPE cell death. Overactivation of **JNK1** and P38 kinase was also observed during pharmacologically induced cell death, suggesting that this process is common to RPE cell-death-signaling pathways induced by various stress stimuli. Cell death mediated by the overactivation of **JNK1** and P38 kinase was cyclin D1- and c-Myc-independent. **CONCLUSIONS:** The inhibition of **JNK1** or P38 kinase had no effect on FCS-stimulated proliferation of RPE cells, whereas the overactivation of these two enzymes was involved in RPE cell death in FCS-depleted cultures. Parallel upstream signaling pathways and cross talk between the two kinases suggest that the regulation of signaling in RPE cell death is complex.

CT *Apoptosis

Blotting, Western

Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism

Cell Division

Cells, Cultured

Down-Regulation

Enzyme Activation

Enzyme Inhibitors: PD, pharmacology

Humans

MAP Kinase Kinase 3

*MAP Kinase Kinase 4

MAP Kinase Kinase 6

*MAP Kinase Signaling System: PH, physiology

Mitogen-Activated Protein Kinase 8

Mitogen-Activated Protein Kinase Kinases: ME, metabolism

Mitogen-Activated Protein Kinases: AI, antagonists & inhibitors

*Mitogen-Activated Protein Kinases: ME, metabolism

Pigment Epithelium of Eye: EN, enzymology***Pigment Epithelium of Eye: PA, pathology**

Protein-Tyrosine Kinase: ME, metabolism

Research Support, Non-U.S. Gov't

p38 Mitogen-Activated Protein Kinases

CN 0 (Enzyme Inhibitors); 0 (MAP Kinase Signaling System); EC 2.7.1.- (MAP Kinase Kinase 3); EC 2.7.1.- (MAP Kinase Kinase 4); EC 2.7.1.- (MAP Kinase Kinase 6); EC 2.7.1.- (MAP2K3 protein, human); EC 2.7.1.- (MAP2K4 protein, human); EC 2.7.1.- (MAP2K6 protein, human); EC 2.7.1.- (Mitogen-Activated Protein Kinase Kinases); EC 2.7.1.112 (Protein-Tyrosine Kinase); EC 2.7.1.123 (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.1.37 (**Mitogen-Activated Protein Kinase 8**); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases)

L640 ANSWER 56 OF 79 MEDLINE on STN

ACCESSION NUMBER: 2005274874 MEDLINE

DOCUMENT NUMBER: PubMed ID: 15878805

TITLE: Signal transduction pathways of nitric oxide release in primary microglial culture challenged with gram-positive bacterial constituent, lipoteichoic acid.

AUTHOR: Chien H F; Yeh K Y; Jiang-Shieh Y F; Wei I H; Chang C Y; Chang M L; Wu C H

CORPORATE SOURCE: Department of Surgery, College of Medicine, National Taiwan University, 1, Section 1, Jen-Ai Road, Taipei 100, Taiwan.

SOURCE: Neuroscience, (2005) 133 (2) 423-36.
Journal code: 7605074. ISSN: 0306-4522.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200508
 ENTRY DATE: Entered STN: 20050527
 Last Updated on STN: 20050831
 Entered Medline: 20050830

ED Entered STN: 20050527

Last Updated on STN: 20050831

Entered Medline: 20050830

AB Between one-third and one-half of all cases of sepsis are known to be caused by gram-positive microorganisms through the cell wall component, e.g. lipoteichoic acid (LTA). Gram-positive bacteria are also known to induce encephalomyelitis and meningeal inflammation, and enhance the production of nitric oxide (NO) via expression of inducible nitric oxide synthase (iNOS) in murine tissue macrophages. It remains to be explored if LTA could activate microglia considered to be resident brain macrophages. We report here that LTA derived from gram-positive bacteria (*Staphylococcus aureus*) significantly induces NO release and iNOS expression in primary microglia. LTA-induced NO accumulation was detected at 2 h in microglial culture and was significantly attenuated by pretreatment with anti-CD14, complement receptor type 3 (CR3) or scavenger receptor (SR) antibodies. LTA activated mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase, p38 MAPK or c-Jun N-terminal kinase in cultured microglia. LTA-elicited microglial NO production was also drastically suppressed by SB203580 (p38 MAPK inhibitor) or pyrrolidine dithiocarbamate (an inhibitor of nuclear factor kappaB), indicating that p38 MAPK and nuclear factor kappaB were involved in microglial NO release after LTA challenge. These results suggest that gram-positive bacterial product such as LTA can activate microglia to release NO via the signal transduction pathway involving multiple LTA receptors (e.g. CD14, CR3 or SR), p38 MAPK and nuclear factor kappaB. The in vivo study further confirmed that administered intracerebrally LTA induced considerable noticeable iNOS, phospho-IkappaB and phospho-p38 MAPK expression in microglia/macrophages.

CT Check Tags: Comparative Study

Animals

Antibodies: PD, pharmacology

Antigens, CD14: IM, immunology

Blotting, Western: MT, methods

Carbidopa: IM, immunology

Cells, Cultured

Dose-Response Relationship, Drug

Drug Combinations

Eye Proteins: IM, immunology

Fluorescent Antibody Technique: MT, methods

Gene Expression Regulation: DE, drug effects

I-kappa B: ME, metabolism

Indoles: DU, diagnostic use

Lectins: ME, metabolism

Levodopa: IM, immunology

*Lipopolysaccharides: PD, pharmacology

*Microglia: DE, drug effects

Microglia: EN, enzymology

Nerve Tissue Proteins: IM, immunology

*Nitric Oxide: ME, metabolism

Nitric-Oxide Synthase: ME, metabolism

Nitrites: ME, metabolism

Rats

Rats, Wistar

Research Support, Non-U.S. Gov't

*Signal Transduction: DE, drug effects

*Teichoic Acids: PD, pharmacology

Time Factors

p38 Mitogen-Activated Protein Kinases: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 38821-49-7 (Carbidopa); 47165-04-8 (DAPI);
56411-57-5 (lipoteichoic acid); 57308-51-7 (Sinemet)

CN 0 (Antibodies); 0 (Antigens, CD14); 0 (Drug Combinations); 0 (**Eye**
Proteins); 0 (I-kappa B); 0 (Indoles); 0 (Lectins); 0 (Levodopa); 0
(Lipopolysaccharides); 0 (Nerve Tissue Proteins); 0 (Nitrites); 0
(Teichoic Acids); 0 (synoretin); EC 1.14.13.39 (Nitric-Oxide Synthase); EC
1.14.13.39 (inducible nitric oxide synthase); EC 2.7.1.37 (p38
Mitogen-Activated Protein Kinases)

L640 ANSWER 57 OF 79 MEDLINE on STN

ACCESSION NUMBER: 2005491979 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 16163009

TITLE: Hyperosmolar saline is a proinflammatory stress on the
mouse **ocular** surface.

AUTHOR: Luo Lihui; Li De-Quan; Corrales Rosa M; Pflugfelder Stephen
C

CORPORATE SOURCE: From the Ocular Surface Center, Cullen Eye Institute,
Department of Ophthalmology, Baylor College of Medicine,
Houston, TX.

SOURCE: Eye & contact lens, (2005 Sep) 31 (5) 186-93.

Journal code: 101160941. ISSN: 1542-2321.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED;
Priority Journals

ENTRY DATE: Entered STN: 20050916

Last Updated on STN: 20050916

ED Entered STN: 20050916

Last Updated on STN: 20050916

AB PURPOSE.: To investigate whether hyperosmolar stress stimulates production
of inflammatory mediators and activates the mitogen-activated protein
kinase (MAPK) signaling pathways, **c-jun n-**
terminal kinases (JNKs), extracellular-regulated kinases
(ERKs), and p38 on the mouse **ocular** surface. METHODS.:
129SvEv/CD-1 mixed mice were treated with a balanced salt solution (BSS)
(305 mOsm) or a hyperosmotic saline solution (HOSS) (500 mOsm). Untreated
age-matched mice were used as controls. The concentrations of interleukin
1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha) were measured
by enzyme-linked immunosorbent assay. Gelatinase activity was determined
by in situ zymography. **Corneal and conjunctival**
epithelia were lysed for Western blot with MAPK antibodies or used for
semiquantitative reverse transcription and polymerase chain reaction and
gene array. RESULTS.: Compared with age-matched controls and mice treated
with BSS, the concentration of IL-1beta in **tear** fluid washings
and the concentrations of IL-1beta and TNF-alpha and gelatinolytic
activity in the **corneal and conjunctival** epithelia
were significantly increased in mice treated with HOSS for 2 days. The
expressions of IL-1beta, TNF-alpha, and matrix metalloproteinase 9 (MMP-9)
messenger RNA by the **corneal and conjunctival**
epithelia were also notably stimulated in mice treated with HOSS. The
levels of phosphorylated **JNK1/2**, **ERK1/2**, and p38 MAPKs in the
corneal and conjunctival epithelia were slightly
increased in mice treated with BSS, but markedly increased in mice treated
with HOSS. CONCLUSIONS.: These results show that the hyperosmolarity
stimulates expression and production of IL-1beta, TNF-alpha, and MMP-9 and
activates JNK, ERK, and p38 MAPK signaling pathways on the mouse

ocular surface. These findings suggest that hyperosmolar stress, as it may occur in dry eye, promotes ocular surface inflammation.

L640 ANSWER 58 OF 79 MEDLINE on STN
 ACCESSION NUMBER: 2004483053 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15452057
 TITLE: Innate immune response of **corneal** epithelial cells to Staphylococcus aureus infection: role of peptidoglycan in stimulating proinflammatory cytokine secretion.
 AUTHOR: Kumar Ashok; Zhang Jing; Yu Fu-Shin X
 CORPORATE SOURCE: Department of Cellular Biology and Anatomy, Medical College of Georgia, Augusta, Georgia 30912, USA.
 CONTRACT NUMBER: EY10869 (NEI)
 EY14080 (NEI)
 SOURCE: Investigative ophthalmology & visual science, (2004 Oct) 45 (10) 3513-22.
 Journal code: 7703701. ISSN: 0146-0404.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200411
 ENTRY DATE: Entered STN: 20040929
 Last Updated on STN: 20041106
 Entered Medline: 20041106
 ED Entered STN: 20040929
 Last Updated on STN: 20041106
 Entered Medline: 20041106
 AB PURPOSE: This study sought to elucidate the innate immune responses of cultured human **corneal** epithelial cells (HCECs) to infection by the Gram-positive bacterium Staphylococcus aureus and to determine the underlying mechanisms. METHODS: HUCL, a telomerase-immortalized HCEC line, and primary cultures of HCECs were challenged with live or heat-killed S. aureus, its exoproducts, or cell wall components lipoteichoic acid (LTA) and peptidoglycan (PGN). IkappaB-alpha phosphorylation and degradation as well as phosphorylation of MAPKs, p38, and JNK-1/2, were assessed by Western blot analysis. The expression of interleukin (IL)-6, IL-8, TNF-alpha, and beta-defensin-2 were determined using RT-PCR and secretion of IL-6, IL-8, TNF-alpha, and beta-defensin were measured using enzyme-linked immunosorbent assay and immunoblot analysis of culture medium. RESULTS: Exposure of HUCL cells to live, but not heat-killed, S. aureus resulted in NF-kappaB activation in a time-dependent manner, as assessed by the increase in IkappaB-alpha phosphorylation and degradation. Live bacteria also activated the p38 and JNK pathways. The effects of live bacteria on HUCL cells may be attributable to bacterial exoproducts, since the conditioned medium of S. aureus also effectively stimulated these signaling pathways. PGN, but not LTA, activated the NF-kappaB and MAPK pathways in a dose- and time-dependent manner. Concomitant with activation of NF-kappaB and MAPKs, transcriptional expression of IL-6, IL-8, TNF-alpha, and beta-defensin-2 were induced in cells challenged with bacterial exoproducts and PGN. Secretion of IL-6, IL-8, TNF-alpha, and beta-defensin-2 were also significantly increased in HCECs in response to bacterial exoproducts and PGN challenge. CONCLUSIONS: **Corneal** epithelial cells possess the ability to recognize the presence of Gram-positive bacteria and to initiate the innate immune responses by the expression and/or release of proinflammatory cytokines and beta-defensin-2 in the **cornea**.

CT Blotting, Western
 Cells, Cultured
 Cytokines: GE, genetics
 *Cytokines: ME, metabolism
 Dose-Response Relationship, Drug
 Epithelium, Corneal: DE, drug effects
 *Epithelium, Corneal: IM, immunology
 *Epithelium, Corneal: MI, microbiology
 Humans
 I-kappa B: ME, metabolism
 *Immunity, Natural
 Lipopolysaccharides: PD, pharmacology
 Mitogen-Activated Protein Kinase 8
 Mitogen-Activated Protein Kinases: ME, metabolism
 *Peptidoglycan: PD, pharmacology
 Phosphorylation
 RNA, Messenger: ME, metabolism
 Research Support, U.S. Gov't, P.H.S.
 Reverse Transcriptase Polymerase Chain Reaction
 *Staphylococcus aureus: PH, physiology
 Teichoic Acids: PD, pharmacology
 Time Factors
 beta-Defensins: ME, metabolism
 p38 Mitogen-Activated Protein Kinases
 RN 139874-52-5 (NF-kappaB inhibitor alpha); 56411-57-5 (lipoteichoic acid)
 CN 0 (Cytokines); 0 (I-kappa B); 0 (Lipopolysaccharides); 0 (Peptidoglycan);
 0 (RNA, Messenger); 0 (Teichoic Acids); 0 (beta-Defensins); 0
 (beta-defensin-2); EC 2.7.1.37 (Mitogen-Activated
 Protein Kinase 8); EC 2.7.1.37
 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated
 Protein Kinases)

L640 ANSWER 59 OF 79 MEDLINE on STN
 ACCESSION NUMBER: 2004284056 MEDLINE
 DOCUMENT NUMBER: PubMed ID: 15184502
 TITLE: Nuclear factor of activated T cells balances angiogenesis
 activation and inhibition.
 AUTHOR: Zaichuk Tetiana A; Shroff Emelyn H; Emmanuel Rebekah;
 Filleur Stephanie; Nelius Thomas; Volpert Olga V
 CORPORATE SOURCE: Department of Urology, Northwestern University Feinberg
 School of Medicine, Chicago, IL 60611, USA.
 CONTRACT NUMBER: R01 HL 68033-04 (NHLBI)
 SOURCE: Journal of experimental medicine, (2004 Jun 7) 199 (11)
 1513-22.
 Journal code: 2985109R. ISSN: 0022-1007.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200408
 ENTRY DATE: Entered STN: 20040609
 Last Updated on STN: 20040825
 Entered Medline: 20040824
 ED Entered STN: 20040609
 Last Updated on STN: 20040825
 Entered Medline: 20040824
 AB It has been demonstrated that vascular endothelial cell growth factor
 (VEGF) induction of angiogenesis requires activation of the nuclear factor
 of activated T cells (NFAT). We show that NFATc2 is also activated by
 basic fibroblast growth factor and blocked by the inhibitor of

angiogenesis pigment epithelial-derived factor (PEDF). This suggests a pivotal role for this transcription factor as a convergence point between stimulatory and inhibitory signals in the regulation of angiogenesis. We identified c-Jun NH2-terminal kinases (JNKs) as essential upstream regulators of NFAT activity in angiogenesis. We distinguished JNK-2 as responsible for NFATc2 cytoplasmic retention by PEDF and JNK-1 and JNK-2 as mediators of PEDF-driven NFAT nuclear export. We identified a novel NFAT target, caspase-8 inhibitor cellular Fas-associated death domain-like interleukin 1beta-converting enzyme inhibitory protein (c-FLIP), whose expression was coregulated by VEGF and PEDF. Chromatin immunoprecipitation showed VEGF-dependent increase of NFATc2 binding to the c-FLIP promoter in vivo, which was attenuated by PEDF. We propose that one possible mechanism of concerted angiogenesis regulation by activators and inhibitors may be modulation of the endothelial cell apoptosis via c-FLIP controlled by NFAT and its upstream regulator JNK.

CT Apoptosis

Carrier Proteins: GE, genetics

Cells, Cultured

DNA: ME, metabolism

*DNA-Binding Proteins: PH, physiology

*Eye Proteins

Humans

*Intracellular Signaling Peptides and Proteins

Mitogen-Activated Protein Kinase 1: PH, physiology

Mitogen-Activated Protein Kinase 3

Mitogen-Activated Protein Kinase 8

Mitogen-Activated Protein Kinase 9

Mitogen-Activated Protein Kinases: PH, physiology

*Neovascularization, Physiologic

*Nerve Growth Factors

*Nuclear Proteins

Phosphorylation

Promoter Regions (Genetics)

Proteins: PH, physiology

Research Support, Non-U.S. Gov't

Research Support, U.S. Gov't, P.H.S.

Serpins: PH, physiology

*Transcription Factors: PH, physiology

p38 Mitogen-Activated Protein Kinases

RN 9007-49-2 (DNA)

CN 0 (CASP8 and FADD-like apoptosis regulating protein); 0 (Carrier Proteins); 0 (DNA-Binding Proteins); 0 (Eye Proteins); 0 (Intracellular Signaling Peptides and Proteins); 0 (Nerve Growth Factors); 0 (Nuclear Proteins); 0 (Proteins); 0 (Serpins); 0 (Transcription Factors); 0 (nuclear factors of activated T-cells); 0 (pigment epithelium-derived factor); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 1); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 3); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 8); EC 2.7.1.37 (Mitogen-Activated Protein Kinase 9); EC 2.7.1.37 (Mitogen-Activated Protein Kinases); EC 2.7.1.37 (p38 Mitogen-Activated Protein Kinases)

L640-ANSWER 60 OF 79 MEDLINE on STN

ACCESSION NUMBER: 2004092816 MEDLINE

DOCUMENT NUMBER: PubMed ID: 14981905

TITLE: Inducible expression of RbAp46 activates c-Jun NH2-terminal kinase-dependent apoptosis and suppresses progressive growth of tumor xenografts in nude mice.

AUTHOR: Zhang Teng-Fei; Yu Shui-Qing; Loggie Brian W; Wang Zhao-Yi

CORPORATE SOURCE: Cancer Center, Creighton University, 2500 California Plaza,

Omaha, NE 68178, USA.
 CONTRACT NUMBER: CA 76632 (NCI)
 CA 84328 (NCI)
 SOURCE: Anticancer research, (2003 Nov-Dec) 23 (6C) 4621-7.
 Journal code: 8102988. ISSN: 0250-7005.
 PUB. COUNTRY: Greece
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200404
 ENTRY DATE: Entered STN: 20040302
 Last Updated on STN: 20040402
 Entered Medline: 20040401

ED Entered STN: 20040302
 Last Updated on STN: 20040402
 Entered Medline: 20040401

AB BACKGROUND: The retinoblastoma (Rb) suppressor-associated protein 46 (RbAp46) is a member of the WD-repeat protein family and a component of histone modifying and remodeling complexes. Previously, we demonstrated that RbAp46 inhibits cell growth and suppresses the transformed phenotypes of tumor cell lines. MATERIALS AND METHODS: We established a tetracycline-inducible RbAp46 expression system in Saos-2 cells to test the effects of RbAp46 induction on cell growth in vitro and on tumor formation in vivo. RESULTS: We found that inducible expression of RbAp46 activated the **c-Jun N-terminal kinase** (JNK) signaling pathway and triggered apoptosis in Saos-2 cells. A dominant-negative mutant of **JNK1**, which can inhibit RbAp46-induced JNK activity, blocked RbAp46-mediated apoptosis. We also found that the induction of RbAp46 expression strongly suppressed the formation of tumors grafted in nude mice and drastically reduced growth of established tumor xenografts. CONCLUSION: These results revealed a novel proapoptotic activity for RbAp46 via the JNK pathway and demonstrated that induction of RbAp46 expression inhibits progressive growth of tumor grafts in vivo.

CT Animals
 *Apoptosis
 Bone Neoplasms: EN, enzymology
 *Bone Neoplasms: PA, pathology
 *Carrier Proteins: GE, genetics
 Carrier Proteins: PH, physiology
 Cell Division
 Enzyme Activation
 Eye Neoplasms: GE, genetics
 Gene Expression Regulation, Neoplastic
 Humans
 JNK Mitogen-Activated Protein Kinases
 Mice
 Mice, Nude
 *Mitogen-Activated Protein Kinases: GE, genetics
 Mitogen-Activated Protein Kinases: ME, metabolism
 *Nuclear Proteins: GE, genetics
 Nuclear Proteins: PH, physiology
 Osteosarcoma: EN, enzymology
 *Osteosarcoma: PA, pathology
 Research Support, U.S. Gov't, P.H.S.
 Retinoblastoma: GE, genetics
 Transplantation, Heterologous

CN 0 (Carrier Proteins); 0 (Nuclear Proteins); 0 (RBBP7 protein, human); 0 (Rbbp7 protein, mouse); EC 2.7.1.37 (JNK Mitogen-Activated Protein Kinases); EC 2.7.1.37 (Mitogen-Activated Protein Kinases)

L640 ANSWER 61 OF 79 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004421836 EMBASE

TITLE: The c-Jun NH(2)-terminal kinase is essential for epidermal growth factor expression during epidermal morphogenesis.

AUTHOR: Weston C.R.; Wong A.; Hall J.P.; Goad M.E.P.; Flavell R.A.; Davis R.J.

CORPORATE SOURCE: R.J. Davis, Howard Hughes Medical Institute, Program in Molecular Medicine, Univ. of MA Medical School, Worcester, MA 01605, United States. roger.davis@umassmed.edu

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (28 Sep 2004) Vol. 101, No. 39, pp. 14114-14119.
Refs: 25
ISSN: 0027-8424 CODEN: PNASA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 021 Developmental Biology and Teratology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20041021
Last Updated on STN: 20041021

ED Entered STN: 20041021
Last Updated on STN: 20041021

AB The c-Jun NH(2)-terminal kinase (JNK) group of mitogen-activated protein kinases is activated in response to a wide array of cellular stresses and proinflammatory cytokines. Roles for JNK in the developing nervous system and T-cell-mediated immunity have been established by detailed studies of mice with compound mutations in the Jnk genes. However, little is known concerning the roles of JNK in other mammalian tissues. Mice lacking both of the ubiquitously expressed isoforms (JNK1 and -2) die during midgestation with neural tube closure defects and brain abnormalities. Here we show that JNK-deficient mice exhibit delayed epithelial development in the epidermis, intestines, and lungs. In addition, JNK-deficient mice exhibit an eyelid closure defect associated with markedly reduced epidermal growth factor (EGF) receptor function, and loss of expression of the ligand EGF. We further demonstrate that adult mice lacking either JNK1 or -2 display striking differences in epidermal proliferation and differentiation, indicative of distinct roles for these kinases in the skin. We conclude that JNK is necessary for epithelial morphogenesis and is an essential regulator of signal transduction by the EGF receptor in the epidermis.

CT Medical Descriptors:
*cell growth
*morphogenesis
*cell maturation
protein expression
epidermis
intestine
lung
epithelium cell
eyelid closure
eye malformation
disease association
protein function
cell proliferation
cell differentiation
survival time

birth
 immaturity
 nonhuman
 mouse
 animal experiment
 controlled study
 animal cell
 article
 priority journal

Drug Descriptors:

*stress activated protein kinase: EC, endogenous compound

*epidermal growth factor: EC, endogenous compound

*epidermal growth factor receptor: EC, endogenous compound

RN (stress activated protein kinase) 155215-87-5; (epidermal growth factor)
 62229-50-9

L640 ANSWER 62 OF 79 EMBASE COPYRIGHT (c) 2005 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003305840 EMBASE

TITLE: Immunohistochemical study for MAPK expression in epidermal tumors related to sun exposure.

AUTHOR: Ko J.H.; Kim J.S.; Choi K.C.; Chung B.S.

CORPORATE SOURCE: Korea, Republic of. bsjung@chosun.ac.kr

SOURCE: Korean Journal of Dermatology, (1 May 2003) Vol. 41, No. 5, pp. 578-585.

Refs: 28

ISSN: 0494-4739 CODEN: TPKCAW

COUNTRY: Korea, Republic of

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 013 Dermatology and Venereology
 016 Cancer

LANGUAGE: Korean

SUMMARY LANGUAGE: English; Korean

ENTRY DATE: Entered STN: 20030814

Last Updated on STN: 20030814

ED Entered STN: 20030814

Last Updated on STN: 20030814

AB Background: Mitogen-activated protein kinase (MAPK) is an important molecule in transducing extracellular signal from cell surface to the nucleus. MAPK family includes ERK (extracellular signal-regulated protein kinase), JNK (stress-activated c-Jun N-terminal kinase), p38 kinases. Not only various growth factors and cytokines, but also other signals such as UV light are able to activate MAPK, resulting in various cellular responses including proliferation, differentiation and apoptosis. Objective: The purpose of our study was to determine patterns of MAPK expression in epidermal tumors including seborrheic keratosis (SK) on sun-exposed skin and unexposed area, actinic keratosis (AK), Bowen's disease (BD), acantholytic squamous cell carcinoma (ASCC), and other squamous cell carcinoma (SCC). Methods: Using pan ERK, JNK-2 and p-JNK, we have examined MAPK expression immunohistochemically in epidermal tumors (total 30 cases) including SK on sun-exposed skin (5 cases) and unexposed areas (5 cases), AK (5 cases), BD (5 cases), ASCC (5 cases), and SCC (5 cases). Results: ERK was expressed in AK and ASCC positively but not in BD, and the staining pattern with ERK also showed positivity in microinvasive area and dysplastic cells of SCC. JNK was not expressed in all tumor cells of SK, AK, BD, and ASCC with the exception of dyskeratotic cells in BD and acantholytic cells in ASCC. Conclusions: We suggest that ERK expression may be related to sun exposure and responsible for proliferation of tumor and invasion into surrounding tissue. JNK may not

be related with malignant progression of tumor and carcinogenesis caused by sun exposure, but with apoptosis of tumor cells.

CT Medical Descriptors:

*skin tumor
 *sun exposure
 protein expression
 immunohistochemistry
 ultraviolet radiation
 enzyme activation
 cell proliferation
 cell differentiation
 apoptosis
 seborrheic keratosis
 actinic keratosis
 Bowen disease
 squamous cell carcinoma
 cancer invasion
 tumor growth
 carcinogenesis
 human
 male
 female
 clinical article
 aged
 child
 adult
 article
 Drug Descriptors:
 *mitogen activated protein kinase
 *stress activated protein kinase
 *growth factor
 *cytokine

RN (mitogen activated protein kinase) 142243-02-5; (stress activated protein kinase) 155215-87-5

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ACCESSION NUMBER: 2003130665. EMBASE

TITLE: Anticancer potential of curcumin: Preclinical and clinical studies.

AUTHOR: Aggarwal B.B.; Kumar A.; Bharti A.C.

CORPORATE SOURCE: B.B. Aggarwal, Cytokine Research Section, Department of Bioimmunotherapy, Univ. Texas M. D. Anderson Cancer C., 1515 Holcombe Boulevard, Houston, TX, United States.
 aggarwal@mdanderson.org

SOURCE: Anticancer Research, (2003) Vol. 23, No. 1 A, pp. 363-398.
 Refs: 337

ISSN: 0250-7005 CODEN: ANTRD4

COUNTRY: Greece

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 016 Cancer
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 20030417

Last Updated on STN: 20030417

ED Entered STN: 20030417

Last Updated on STN: 20030417

AB Curcumin (diferuloylmethane) is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Extensive research over the last 50 years has indicated this polyphenol can both prevent and treat cancer. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, down-regulate transcription factors NF- κ B, AP-1 and Egr-1; down-regulate the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2); and inhibit the activity of c-**Jun N-terminal kinase**, protein tyrosine kinases and protein serine/threonine kinases. In several systems, curcumin has been described as a potent antioxidant and anti-inflammatory agent. Evidence has also been presented to suggest that curcumin can suppress tumor initiation, promotion and metastasis. Pharmacologically, curcumin has been found to be safe. Human clinical trials indicated no dose-limiting toxicity when administered at doses up to 10 g/day. All of these studies suggest that curcumin has enormous potential in the prevention and therapy of cancer. The current review describes in detail the data supporting these studies.

CT Medical Descriptors:
 *antineoplastic activity
 *drug screening
 drug isolation
 cancer therapy
 cell proliferation
 tumor cell
 down regulation
 gene activity
 antioxidant activity
 antiinflammatory activity
 drug mechanism
 toxicity: SI, side effect
 dose response
 drug structure
 structure activity relation
 gene repression
 multigene family
 drug protein binding
 drug receptor binding
 drug transformation
 drug distribution
 drug metabolism
 drug clearance
 drug excretion
 drug blood level
 eye disease: SI, side effect
 retina macula edema: SI, side effect
 cataract: SI, side effect
 side effect: SI, side effect
 glaucoma: SI, side effect
 optic nerve lesion: SI, side effect
 orbit pseudotumor: DT, drug therapy
 intestine cancer: DT, drug therapy
 oncogene neu
 human
 nonhuman
 clinical trial
 review
 priority journal
 Drug Descriptors:

*curcumin: AE, adverse drug reaction
 *curcumin: CT, clinical trial
 *curcumin: AD, drug administration
 *curcumin: AN, drug analysis
 *curcumin: CR, drug concentration
 *curcumin: DV, drug development
 *curcumin: DO, drug dose
 *curcumin: DT, drug therapy
 *curcumin: PK, pharmacokinetics
 *curcumin: PD, pharmacology
 *curcumin: IP, intraperitoneal drug administration
 *curcumin: IV, intravenous drug administration
 *curcumin: PO, oral drug administration
 corticosteroid: CM, drug comparison
 cyclooxygenase 2: EC, endogenous compound
 nitric oxide synthase: EC, endogenous compound
 gelatinase B: EC, endogenous compound
 tumor necrosis factor: EC, endogenous compound
 chemokine: EC, endogenous compound
 epidermal growth factor receptor: EC, endogenous compound
 stress activated protein kinase: EC, endogenous compound
 protein tyrosine kinase: EC, endogenous compound
 protein serine threonine kinase: EC, endogenous compound
 lipoxxygenase: EC, endogenous compound
 urokinase: EC, endogenous compound
 RN (curcumin) 458-37-7; (nitric oxide synthase) 125978-95-2; (gelatinase B) 146480-36-6; (stress activated protein kinase) 155215-87-5; (protein tyrosine kinase) 80449-02-1; (lipoxxygenase) 9027-17-2, 9029-60-1; (urokinase) 139639-24-0

L640 ANSWER 64 OF 79 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

ACCESSION NUMBER: 2004:320309 BIOSIS
 DOCUMENT NUMBER: PREV200400321106
 TITLE: Wounding induces motility in sheets of **corneal** epithelial cells through loss of spatial constraints - Role of heparin-binding epidermal growth factor-like growth factor signaling.
 AUTHOR(S): Block, Ethan R.; Matela, Abigail R.; SundarRaj, Nirmala; Iszkula, Erik R.; Klarlund, Jes K. [Reprint Author]
 CORPORATE SOURCE: Sch MedDept Ophthalmol, Univ Pittsburgh, 203 Lothrop St, Pittsburgh, PA, 15213, USA
 klarlundjk@upmc.edu
 SOURCE: Journal of Biological Chemistry, (June 4 2004) Vol. 279, No. 23, pp. 24307-24312. print.
 CODEN: JBCHA3. ISSN: 0021-9258.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 ENTRY DATE: Entered STN: 21 Jul 2004
 Last Updated on STN: 21 Jul 2004
 ED Entered STN: 21 Jul 2004
 Last Updated on STN: 21 Jul 2004
 AB Cellular responses to wounding have often been studied at a molecular level after disrupting cell layers by mechanical means. This invariably results in damage to cells at the edges of the wounds, which has been suggested to be instrumental for initiating wound healing. To test this, we devised an alternative procedure to introduce gaps in layers of **corneal** epithelial cells by casting agarose strips on tissue culture plates. In contrast to mechanical wounding, removal of the strips did not lead to detectable membrane leakage or to activation of the

stress-activated kinase JNK. Nonetheless, cells at the edge underwent the typical morphological transition to a highly motile phenotype, and the gaps closed at rates similar to those of mechanically induced wounds. To allow biochemical analysis of cell extracts, a procedure was devised that makes cell-free surface area acutely available to a large proportion of cells in culture. Rapid activation of the epidermal growth factor receptor (EGFR) was detected by immunoblotting, and the addition of an EGFR-blocking antibody completely abolished wound healing. In addition, wound healing was inhibited by agents that block signaling by the heparin-binding epidermal growth factor-like growth factor (HB-EGF). Cells stimulated with cell-free tissue culture surface released a soluble factor that induced activation of the EGFR, which was distinct from HB-EGF. These studies suggest that the triggering event for the induction of motility in corneal epithelial cells is related to the sudden availability of permissive surface area rather than to mechanical damage, and they demonstrate a central role of signaling through HB-EGF.

CC Cytology - General 02502
 Cytology - Animal 02506
 Biochemistry studies - General 10060
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004

IT Major Concepts
 Biochemistry and Molecular Biophysics; Cell Biology; Sense Organs
 (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
 corneal epithelial cells: sensory system; eye:
 sensory system

IT Chemicals & Biochemicals
 JNK [c-Jun N-terminal
 kinase]: stress-activated kinase; epidermal growth factor;
 epidermal growth factor receptor: activation; heparin-binding epidermal
 growth factor-like growth factor: signaling

IT Methods & Equipment
 immunoblot: immunologic techniques, laboratory techniques

IT Miscellaneous Descriptors
 cell motility: induction; cellular wounding responses; membrane
 leakage; spatial constraint loss

ORGN Classifier
 Leporidae 86040
 Super Taxa
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rabbit (common): animal model
 Taxa Notes
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman
 Mammals, Vertebrates

RN 155215-87-5 (JNK)
 155215-87-5 (c-Jun N-terminal
 kinase)
 62229-50-9 (epidermal growth factor)
 154531-34-7 (heparin-binding epidermal growth factor-like growth factor)

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ACCESSION NUMBER: 2004:350308 BIOSIS

DOCUMENT NUMBER: PREV200400348029

TITLE: Coordinate signaling by Src and p38 kinases in the
 induction of cortical cataracts.

AUTHOR(S): Zhou, Jian; Menko, A. Sue [Reprint Author]

CORPORATE SOURCE: Dept Pathol Anat and Cell Biol, Thomas Jefferson Univ, 571 Jefferson Alumni Hall, 1020 Locust St, Philadelphia, PA, 19107, USA
sue.menko@jefferson.edu

SOURCE: IOVS, (July 2004) Vol. 45, No. 7, pp. 2314-2323. print.

DOCUMENT TYPE: Article

LANGUAGE: English

ENTRY DATE: Entered STN: 18 Aug 2004
Last Updated on STN: 18 Aug 2004

ED Entered STN: 18 Aug 2004
Last Updated on STN: 18 Aug 2004

AB PURPOSE. The goals of this study were to determine whether MAP kinase signaling pathways play a role in the formation of lens cataracts and to examine the potential signaling relationship between Src and MAP kinases in signaling the induction of lens opacities. METHODS. Embryonic day (E) 10 chick lenses were cultured in Medium 199 containing 10% fetal bovine serum. The activation state of Src kinases and the MAP kinases extracellular signal-regulated protein kinase (ERK), c-jun N-terminal kinase (JNK), and p38 in the lens epithelium was determined over a time course from 10 minutes to 10 days in culture by immunoblot analysis. Src kinase activation was suppressed by exposure to the Src family kinase-specific inhibitor PP1. To examine the role of specific MAP kinases in the development of lens opacities, lenses were grown for 10 days in the presence or absence of inhibitors of ERK (U0126), JNK (SP600125), and p38 (SB203580). Lenses were observed and photographed daily, and the degree of opacification was quantified by using image-analysis software. RESULTS. Within a short time after placing embryonic lenses in culture conditions that induce the formation of cataracts, there occurred a great increase in the activation state of the MAP kinase ERK. Activation of ERK was both rapid and transient. No activation of the MAP kinase JNK was observed in the cataract cultures beyond that which occurred in normal lens epithelium, even though JNK activation is often linked to the cellular response to stress. In contrast, although p38 activation was barely detected in the normal embryonic lens, this stress-activated protein kinase exhibited a robust activation in cataract cultures that was sustained throughout the culture period. Studies conducted to map the cataract signaling pathways indicate that the p38 MAP kinase functions upstream of the Src kinase. To analyze the potential role of ERK, JNK, and p38 in cataract induction, lenses were cultured in the presence of specific MAP kinase inhibitors. Although the inhibitors of ERK and JNK did not interfere with the formation of cataract, p38 inhibitors blocked the development of lens opacities with an efficacy similar to that of the Src kinase inhibitor PP1. CONCLUSIONS. Activation of both Src and p38 kinases lead to the induction of cataract.

CC Biochemistry studies - General 10060
Enzymes - General and comparative studies: coenzymes 10802
Sense organs - Physiology and biochemistry 20004
Sense organs - Pathology 20006
Development and Embryology - General and descriptive 25502

IT Major Concepts
Biochemistry and Molecular Biophysics; Sense Organs (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
lens: sensory system; lens epithelium: sensory system

IT Diseases
corneal cataract: eye disease

IT Chemicals & Biochemicals
MAP kinase [EC 2.7.1.37]; PP1; Src kinase [EC 2.7.1.112]: suppression;
c-jun N-terminal kinase
[EC 2.7.1.112]; extracellular signal-regulated protein kinase [EC

2.7.1.37]; p38
 IT Methods & Equipment
 immunoblot analysis: immunologic techniques, laboratory techniques
 ORGN Classifier
 Galliformes 85536
 Super Taxa
 Aves; Vertebrata; Chordata; Animalia
 Organism Name
 chicken (common): embryo
 Taxa Notes
 Animals, Birds, Chordates, Nonhuman Vertebrates, Vertebrates
 RN 142243-02-5 (MAP kinase)
 9026-43-1 (MAP kinase)
 142243-02-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)
 141349-89-5 (Src kinase)
 80449-02-1 (Src kinase)
 141349-89-5 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 155215-87-5 (c-jun N-terminal
 kinase)
 80449-02-1 (c-jun N-terminal
 kinase)
 155215-87-5 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 142243-02-5 (extracellular signal-regulated protein kinase)
 9026-43-1 (extracellular signal-regulated protein kinase)
 142243-02-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)

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ACCESSION NUMBER: 2003:543913 BIOSIS
 DOCUMENT NUMBER: PREV200300539415
 TITLE: ROLE OF THE C - JUN N -
 TERMINAL KINASE (JNK) IN THE
 CORNEAL EPITHELIAL WOUND HEALING.
 AUTHOR(S): Okada, Y. [Reprint Author]; Saika, S. [Reprint Author];
 Shirai, K. [Reprint Author]; Miyamoto, T. [Reprint Author];
 Yamanaka, O. [Reprint Author]; Ohnishi, Y. [Reprint Author]
 CORPORATE SOURCE: Department of Ophthalmology, Wakayama Medical University,
 Wakayama, Japan
 SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
 (2003) Vol. 2003, pp. Abstract No. 3838. cd-rom.
 Meeting Info.: Annual Meeting of the Association for
 Research in Vision and Ophthalmology. Fort Lauderdale, FL,
 USA. May 04-08, 2003. Association for Research in Vision
 and Ophthalmology.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 19 Nov 2003
 Last Updated on STN: 19 Nov 2003
 ED Entered STN: 19 Nov 2003
 Last Updated on STN: 19 Nov 2003
 AB Purpose: We previously demonstrated that AP-1 is transiently up-regulated
 in healing corneal epithelium following epithelial debridement.
 In response to stress stimuli or cytokine exposure, dual Thr- and
 Tyr-phosphorylations of c-Jun N-
 terminal kinase (JNK) result in its activation and in

further activation of transcription factors including c-Jun. Here we examined the role of JNK in **corneal** epithelial wound healing. Methods: 1) A central epithelial defect in one **cornea** of C57BL/6 mice (n=19) were allowed to heal. Animals were killed and the frozen sections of the affected **eye** were immunostained with an anti-phospho-JNK antibody. 2) Mouse **eye** globes with a central **corneal** epithelial defect (n=26) were incubated for 6 - 48h in culture medium with or without a JNK inhibitor (5.0 mM) and closure of the defect was evaluated. 3) **Corneal** blocks (2x4mm) obtained from a rabbit **cornea** were incubated for 24h with or without the inhibitor. Epithelial spreading on stromal cut surface was histologically measured. Results: 1) No or very faint immunoreaction for JNK was detected in uninjured epithelium. Three to 24h after the treatment, phospho-JNK immunoreactivity was detected in the epithelium surrounding the defect of mouse **corneas**. 2) Adding a JNK inhibitor to the medium retarded the closure of the defect approximately 35% less than control at both 18 and 24 hr cultures in mouse **corneas** (p<0.05). 3) In culture of rabbit corneal blocks, addition of the JNK inhibitor decreased epithelial spreading to around 65% of control (p<0.01). Conclusions: Signaling cascade involving phosphorylated JNK may have an important role in epithelial cell migration during wound healing.

CC General biology - Symposia, transactions and proceedings 00520
 Enzymes - General and comparative studies: coenzymes 10802
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006
 IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs
 (Sensory Reception)
 IT Parts, Structures, & Systems of Organisms
 cornea: sensory system; **corneal** epithelium: sensory
 system
 IT Diseases
 corneal epithelial wound: **eye** disease
 IT Chemicals & Biochemicals
 c-Jun; **c-Jun N-terminal**
 kinase [JNK]: expression
 IT Miscellaneous Descriptors
 corneal epithelial wound healing; epithelial cell migration
 ORGN Classifier
 Leporidae 86040
 Super Taxa
 Lagomorpha; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 rabbit (common)
 Taxa Notes
 Animals, Chordates, Lagomorphs, Mammals, Nonhuman Vertebrates, Nonhuman
 Mammals, Vertebrates
 ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 C57BL/6 mouse (common)
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
 Rodents, Vertebrates
 RN 155215-87-5 (**c-Jun N-terminal**
kinase)
 155215-87-5 (JNK)

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ACCESSION NUMBER: 2003:529013 BIOSIS

DOCUMENT NUMBER: PREV200300524818

TITLE: DOXYCYCLINE INHIBITS TGF - beta1 STIMULATED MMP - 9 IN
HUMAN CORNEAL EPITHELIAL CELLS VIA SMAD AND MAPK
PATHWAYS.

AUTHOR(S): Pflugfelder, S. C. [Reprint Author]; Kim, H. -S. [Reprint
Author]; Li, D. -Q. [Reprint Author]

CORPORATE SOURCE: Ophthalmology-Ocular Surf Ctr, Cullen Eye Institute,
Houston, TX, USA

SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
(2003) Vol. 2003, pp. Abstract No. 1404. cd-rom.
Meeting Info.: Annual Meeting of the Association for
Research in Vision and Ophthalmology. Fort Lauderdale, FL,
USA. May 04-08, 2003. Association for Research in Vision
and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Nov 2003

Last Updated on STN: 12 Nov 2003

ED Entered STN: 12 Nov 2003

Last Updated on STN: 12 Nov 2003

AB Purpose: To evaluate the effects of doxycycline on the expression of
TGF-beta1 stimulated matrix metalloproteinase 9 (MMP-9) in human
corneal epithelial cells and on the activation of Smad2, c
-Jun N-terminal kinase (JNK) and
extracellular-regulated kinase (ERK) signaling intermediates that are
induced by TGF-beta1. Methods: Primary human corneal epithelial
cells were cultured from limbal explants in 6-well plates until
confluence. The cells were then exposed to serum-free media alone
(control), or with different concentrations of TGF-beta1 (0.1, 1, 10 ng/ml)
with or without TGF-beta1 neutralizing mAb (5 mug/ml), SB202190 (10-40
muM) and doxycycline (5-40 mug/ml) for different lengths of time. The
conditioned media were collected from cultures treated for 24 hours for
zymography and MMP-9 activity assay. The cells treated for 5-60 min were
lysed in RIPA buffer and subjected to Western blot with phospho-specific
antibodies against Smad2, JNK or ERK. Results: TGF-beta1 dose-dependently
increased the production and activity of MMP-9 by human corneal
epithelial cells. This stimulation was abolished by 5 mug/ml of TGF-beta1
neutralizing mAb or 10 mug/ml of doxycycline. TGF-beta1 dose-dependently
induced phosphorylated JNK1/2, ERK and Smad2, as early as 5
min, peaking at 15 or 30 min respectively. Doxycycline markedly inhibited
the TGF-beta1 induced activation of JNK1/2, ERK1 and Smad2 with
activity equal to SB202190. Conclusions: Doxycycline inhibits TGF-beta1
induced MMP-9 production and activity, perhaps through the Smad and MAPK
pathways. This finding may explain the reported efficacy of doxycycline
in treating MMP-mediated ocular surface disease.

CC General biology - Symposia, transactions and proceedings 00520

Cytology - Animal 02506

Cytology - Human 02508

Biochemistry studies - General 10060

Biochemistry studies - Proteins, peptides and amino acids 10064

Enzymes - General and comparative studies: coenzymes 10802

Pathology - Therapy 12512

Endocrine - General 17002

Sense organs - Physiology and biochemistry 20004

Pharmacology - General 22002

Pharmacology - Clinical pharmacology 22005

Pharmacology - Sense organs, associated structures and functions 22031

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology
(Biochemistry and Molecular Biophysics); Pharmacology; Sense Organs
(Sensory Reception)

IT Parts, Structures, & Systems of Organisms
corneal epithelial cell: sensory system

IT Chemicals & Biochemicals
MAPK [mitogen-activated protein kinase]; TGF-beta-1 [transforming
growth factor-beta-1]; c-Jun amino-terminal kinase [JNK] [EC
2.7.1.112]; doxycycline: enzyme inhibitor-drug, ophthalmic
-drug, pharmacodynamics; extracellular signal-regulated kinase [ERK];
matrix metalloproteinase-9 [MMP-9]: expression, regulation

IT Miscellaneous Descriptors
MAPK signaling pathway [mitogen-activated protein kinase signaling
pathway]: activation; Smad2 signaling pathway: activation

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 142243-02-5 (MAPK)
142243-02-5 (mitogen-activated protein kinase)
155215-87-5 (c-Jun amino-terminal kinase)
80449-02-1 (c-Jun amino-terminal kinase)
155215-87-5 (JNK)
80449-02-1 (JNK)
155215-87-5 (EC 2.7.1.112)
80449-02-1 (EC 2.7.1.112)
564-25-0 (doxycycline)
142243-02-5 (extracellular signal-regulated kinase)
142243-02-5 (ERK)
146480-36-6 (matrix metalloproteinase-9)
146480-36-6 (MMP-9)

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ACCESSION NUMBER: 2003:528982 BIOSIS

DOCUMENT NUMBER: PREV200300524787

TITLE: JNK PATHWAY ACTIVATION AND APOPTOSIS IN CORNEAL
EPITHELIAL CELLS AFTER ULTRAVIOLET IRRADIATION OF THE RAT
EYE.

AUTHOR(S): Igarashi, S. [Reprint Author]; Takeda, M. [Reprint Author];
Takamiya, A. [Reprint Author]; Yoshida, A. [Reprint Author]

CORPORATE SOURCE: Ophthalmology, Asahikawa Medical College, Asahikawa, Japan
SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
(2003) Vol. 2003, pp. Abstract No. 1373. cd-rom.
Meeting Info.: Annual Meeting of the Association for
Research in Vision and Ophthalmology. Fort Lauderdale, FL,
USA. May 04-08, 2003. Association for Research in Vision
and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Nov 2003

Last Updated on STN: 12 Nov 2003

ED Entered STN: 12 Nov 2003

Last Updated on STN: 12 Nov 2003

- AB Purpose: The **c-Jun N-terminal kinase** (JNK; also known as SAPK, stress activated protein kinase) signaling pathway is activated by cytotoxic stress. To investigate in vivo ultraviolet (UV) irradiation induced JNK pathway activation in **corneal** epithelial cells, the expression of JNK, apoptosis signal-regulating kinase 1 (ASK1), SAPK/ERK kinase (SEK1) and cytochrome c was analyzed in the **cornea**. Methods: **Eyes** of anaesthetized rats were exposed to 0.47J/cm² of ultraviolet radiation (302nm), and expression of **JNK1/2**, ASK1, SEK1, and cytochrome C in **corneal** epithelial cells was examined by protein immunoblot analysis. Histopathology (TUNEL method) and immunohistochemistry for JNK were also performed. Results: **Corneas** exposed to UV radiation showed TUNEL positive staining in epithelial cells and superficial **keratocytes** at 1 hours after irradiation. After UV radiation, substantial expression of activated **JNK1/2** was observed in **corneal** epithelial cells, whereas no expression of activated **JNK1/2** was seen in non-irradiated contralateral **corneas**. The expression of ASK1, SEK1, and cytochrome C was also quickly upregulated in **corneal** epithelial cells after UV exposure. Conclusions: These data suggest that JNK and cytochrome c mediated death pathway may play an important role in UV-induced apoptosis of **corneal** epithelial cells.
- CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506
Radiation biology - General 06502
Enzymes - General and comparative studies: coenzymes 10802
Sense organs - Physiology and biochemistry 20004
- IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Radiation Biology;
Sense Organs (Sensory Reception)
- IT Parts, Structures, & Systems of Organisms
cornea: sensory system; **corneal** epithelial cell:
sensory system; **eyes**: sensory system
- IT Chemicals & Biochemicals
SAPK/ERK kinase [SEK1]: expression, regulation; apoptosis
signal-regulating kinase 1 [ASK1]: expression, regulation; c-Jun
amino-terminal kinase [JNK] [EC 2.7.1.112]: expression, regulation;
cytochrome c: expression, regulation
- IT Methods & Equipment
UV irradiation: laboratory techniques
- IT Miscellaneous Descriptors
c-Jun amino-terminal kinase pathway [JNK pathway]: activation; cell
apoptosis
- ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
Rodents, Vertebrates
- RN 185464-61-3 (apoptosis signal-regulating kinase 1)
185464-61-3 (ASK1)
155215-87-5 (c-Jun amino-terminal kinase)
80449-02-1 (c-Jun amino-terminal kinase)
155215-87-5 (JNK)
80449-02-1 (JNK)
155215-87-5 (EC 2.7.1.112)

80449-02-1 (EC 2.7.1.112)
9007-43-6 (cytochrome c)

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ACCESSION NUMBER: 2003:518264 BIOSIS

DOCUMENT NUMBER: PREV200300512502

TITLE: THE UVB - ELICITED INDUCTION OF MMP - 1 IN PTERYGIUM
EPITHELIAL CELLS IS MEDIATED THROUGH A MAPK - DEPENDENT
PATHWAY.

AUTHOR(S): Di Girolamo, N. [Reprint Author]; Coroneo, M. T.;
Wakefield, D. [Reprint Author]

CORPORATE SOURCE: Sch of Med Sci - Pathology Dept, University of New South
Wales, Sydney, Australia

SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
(2003) Vol. 2003, pp. Abstract No. 1322. cd-rom.
(Meeting Info.: Annual Meeting of the Association for
Research in Vision and Ophthalmology. Fort Lauderdale, FL,
USA. May 04-08, 2003. Association for Research in Vision
and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LANGUAGE: English

ENTRY DATE: Entered STN: 5 Nov 2003

Last Updated on STN: 5 Nov 2003

ED Entered STN: 5 Nov 2003

Last Updated on STN: 5 Nov 2003

AB Purpose: Pterygia are common lesions of the ocular surface
characterized by tissue remodeling, proliferation, angiogenesis and
inflammation. Extensive epidemiological evidence implicates ultraviolet
(UV) light in the pathogenesis of this disease. In this study we
investigated the effect of UV radiation on the expression of MMP-1 in
pterygia and relevant ocular surface epithelial cells.
Methods: Immunohistochemistry was performed on pterygium,
conjunctival, limbal and corneal tissue specimens for
MMP-1 and p63 expression. Primary cultures of pterygium,
conjunctival, and limbal epithelial cells were established,
expanded, and exposed to varying amounts of UVB. Cell and tissue-derived
supernatants and total RNA was harvested and analyzed by Western blotting,
gelatin zymography and RT-PCR for MMP and TIMP expression.
Results: Enhanced expression of MMP-1 protein was observed in pterygium as
compared to conjunctival, limbal, and corneal
specimens. Interestingly, p63 immunoreactivity co-localized with MMP-1
positive epithelium. A dose and time-dependent increase in MMP-1 protein
and mRNA was noted when pterygium and limbal but not conjunctival
epithelial cells were exposed to UVB. Furthermore, MMP-2, MMP-9 and the
TIMPs were not modulated by this treatment. MMP-1 was also enhanced in
UVB-irradiated pterygium specimens. The induction of MMP-1 was not
mediated by a soluble factor but was significantly inhibited with PD98059,
a specific inhibitor of the ERK1/2 MAPK pathway. While SB203580, an
inhibitor of JNK and p38 MAPK pathways had no effect on MMP-1 following
UVB-irradiation. Conclusions: Collectively, these data support the
hypothesis of the likely involvement of UV light and MMPs in the
development of pterygia and imply that ocular protection from UV
light may be one form of disease prevention.

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Animal 02506

Biochemistry studies - Nucleic acids, purines and pyrimidines 10062

Biochemistry studies - Proteins, peptides and amino acids 10064

Enzymes - General and comparative studies: coenzymes 10802
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006
 Tissue culture, apparatus, methods and media 32500

IT Major Concepts
 Enzymology (Biochemistry and Molecular Biophysics); Sense Organs
 (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
conjunctiva: sensory system; **cornea**: sensory
 system; limbal epithelial cells: sensory system; **ocular**
 surface epithelial cells: sensory system

IT Diseases
 pterygium: **eye** disease, etiology
 Pterygium (MeSH)

IT Chemicals & Biochemicals
 ERK1/2 [extracellular signal-regulated kinase 1/2]; JNK [c-
Jun N-terminal kinase]:
 regulation; MMP-1 [matrix metalloproteinase-1]: immunoreactivity,
 expression, regulation; MMP-1 mRNA [matrix metalloproteinase-1
 messenger RNA]; PD98059: enzyme inhibitor-drug; SB203580: enzyme
 inhibitor-drug; TIMP [tissue inhibitor of metalloproteinase]:
 expression, regulation; p38 MAPK [p38 mitogen-activated protein
 kinase]: regulation; p63: immunoreactivity, expression, regulation;
 total RNA

IT Methods & Equipment
 RT-PCR [reverse transcriptase-polymerase chain reaction]: genetic
 techniques, laboratory techniques; Western blotting: genetic
 techniques, laboratory techniques; gelatin zymography: clinical
 techniques, diagnostic techniques; immunohistochemistry: immunologic
 techniques, laboratory techniques; primary culture: culturing
 techniques, laboratory techniques

IT Miscellaneous Descriptors
 UVB radiation

RN 155215-87-5 (JNK)
 155215-87-5 (c-**Jun N-terminal**
kinase)
 9001-12-1 (MMP-1)
 9001-12-1 (matrix metalloproteinase-1)
 167869-21-8 (PD98059)
 152121-47-6 (SB203580)
 86102-31-0 (TIMP)
 86102-31-0 (tissue inhibitor of metalloproteinase)
 165245-96-5 (p38 MAPK)
 165245-96-5 (p38 mitogen-activated protein kinase)

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ACCESSION NUMBER: 2003:529209 BIOSIS
 DOCUMENT NUMBER: PREV200300524947
 TITLE: EXPERIMENTAL **DRY EYE** INDUCED EXPRESSION
 OF INFLAMMATORY CYTOKINES (IL - 1beta AND TNF - alpha) ,
 MMP - 9 AND ACTIVATED MAPK BY THE **CORNEAL**
 EPITHELIUM.
 AUTHOR(S): Luo, L. [Reprint Author]; Li, D. -Q. [Reprint Author];
 Doshi, A. [Reprint Author]; Farley, W. [Reprint Author];
 Pflugfelder, S. [Reprint Author]
 CORPORATE SOURCE: Ophthalmology, Baylor College of Medicine, Houston, TX, USA
 SOURCE: ARVO Annual Meeting Abstract Search and Program Planner,
 (2003) Vol. 2003, pp. Abstract No. 1026. cd-rom.
 Meeting Info.: Annual Meeting of the Association for

Research in Vision and Ophthalmology. Fort Lauderdale, FL, USA. May 04-08, 2003. Association for Research in Vision and Ophthalmology.

DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English

ENTRY DATE: Entered STN: 12 Nov 2003
Last Updated on STN: 12 Nov 2003

ED Entered STN: 12 Nov 2003
Last Updated on STN: 12 Nov 2003

AB Purpose: To investigate the expression of inflammatory cytokines, Interleukin-1 beta (IL-beta) and tumor necrosis factor (TNF-alpha), matrix metalloproteinase 9 (MMP-9) and the activated mitogen-activated protein kinases (MAPK), **c-jun N-terminal kinase (JNK)** extracellular-regulated kinase (ERK) and p38, by **ocular surface** in experimental **dry eye** mice.
Methods: 129SvEv/CD-1 mixed white mice aged 6-8 weeks were treated with systemic scopolamine and exposure to an air draft for 7 days, or treated with hypertonic saline drops (500 mOsm) 6 times/day for 2 days. Untreated mice were used as controls. **Tears** were collected for ELISA and zymography. **Corneal** epithelia were lysed in RIPA buffer for Western blot with phospho-MAPK antibodies, or lysed in 4M guanidium thiocyanate solution for total RNA extraction and subjected to semi-quantitative RT-PCR for gene expression with mouse specific primers for IL-1beta, TNF-alpha, MMP-9 and GAPDH, the latter as a loading control. Results: Compared with age matched controls, the concentrations of IL-1beta and TNF-alpha measured by ELISA and MMP-9 by zymography in the **tear** fluid were significantly increased in 7-day treated **dry eye** mice. Detected by RT-PCR, the expression of IL-1beta, TNF-alpha and MMP-9 mRNA by **corneal** epithelia were also significantly induced in 7-day treated **dry eye** mice. Western blots revealed that phosphorylated **JNK1/2**, **ERK1/2** and p38 were markedly increased in **corneal** epithelia of these **dry eye** mice. Interestingly, two-day treatment with hypertonic saline also stimulated IL-1beta and MMP-9 proteins in **tears** and their mRNA in **corneal** epithelia, as well as activation of **JNK1/2**, **ERK1/2** and p38 signaling pathways in **corneal** epithelia compared with untreated control mice. Conclusions: It was demonstrated that Experimental **dry eye** and exposure to hypertonic saline increases expression and production of IL-1beta, TNF-alpha and MMP-9 as well as MAPK signaling pathways in the **corneal** epithelia. These findings establish a link between the hyperosmolar **tear** film of **dry eye** and the induction of **ocular surface** inflammation in **keratoconjunctivitis Sicca**.

CC General biology - Symposia, transactions and proceedings 00520
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Enzymes - General and comparative studies: coenzymes 10802
Endocrine - General 17002
Sense organs - Physiology and biochemistry 20004
Sense organs - Pathology 20006

IT Major Concepts
Biochemistry and Molecular Biophysics; Sense Organs (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
corneal epithelium: sensory system; **eye**: sensory system

IT Diseases
keratoconjunctivitis Sicca: **eye** disease
Keratoconjunctivitis Sicca (MeSH)

IT Diseases
 ocular surface inflammation: eye disease

IT Chemicals & Biochemicals
 GADPH; c-jun N-terminal
 kinase [EC 2.7.1.112]; extracellular signal-regulated kinase
 [ERK]; gene: expression; guanidium thiocyanate; interleukin-1-beta
 [IL-1-beta]; interleukin-1-beta mRNA [IL-1-beta messenger RNA]; matrix
 metalloproteinase-9 [MMP-9]; matrix metalloproteinase-9 mRNA [MMP-9
 messenger RNA]; mitogen-activated protein kinase [EC 2.7.1.37];
 mitogen-activated protein kinase antibody [MAPK antibody]; p38;
 scopolamine; tumor necrosis factor-alpha [TNF-alpha]; tumor necrosis
 factor-alpha mRNA [TNF-alpha messenger RNA]

ORGN Classifier
 Muridae 86375
 Super Taxa
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 mouse (common)
 Taxa Notes
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,
 Rodents, Vertebrates

RN 155215-87-5 (c-jun N-terminal
 kinase)
 80449-02-1 (c-jun N-terminal
 kinase)
 155215-87-5 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 142243-02-5 (extracellular signal-regulated kinase)
 142243-02-5 (ERK)
 146480-36-6 (matrix metalloproteinase-9)
 146480-36-6 (MMP-9)
 142243-02-5 (mitogen-activated protein kinase)
 9026-43-1 (mitogen-activated protein kinase)
 142243-02-5 (EC 2.7.1.37)
 9026-43-1 (EC 2.7.1.37)
 51-34-3 (scopolamine)

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ACCESSION NUMBER: 2003:566860 BIOSIS
 DOCUMENT NUMBER: PREV200300563876
 TITLE: Role of ocular surface inflammation in the
 pathogenesis of keratoconjunctivitis sicca.
 AUTHOR(S): Pflugfelder, S. C. [Reprint Author]; Li, D. Q. [Reprint
 Author]; Farley, W. [Reprint Author]; Stern, M. E.
 CORPORATE SOURCE: Cullen Eye Institute, Baylor College of Medicine, 6565
 Fannin, NC 205, Houston, TX, 77030, USA
 SOURCE: Inflammation Research, (July 2003) Vol. 52, No. Supplement
 2, pp. S 90. print.
 Meeting Info.: 6th World Congress on Inflammation.
 Vancouver, British Columbia, Canada. August 02-06, 2003.
 International Association of Inflammation Societies.
 ISSN: 1023-3830.
 DOCUMENT TYPE: Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 LANGUAGE: English
 ENTRY DATE: Entered STN: 3 Dec 2003
 Last Updated on STN: 3 Dec 2003
 ED Entered STN: 3 Dec 2003
 Last Updated on STN: 3 Dec 2003

CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Animal 02506
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Enzymes - General and comparative studies: coenzymes 10802
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Endocrine - General 17002
 Sense organs - Physiology and biochemistry 20004
 Sense organs - Pathology 20006
 Immunology - General and methods 34502

IT Major Concepts
 Immune System (Chemical Coordination and Homeostasis); Sense Organs
 (Sensory Reception)

IT Parts, Structures, & Systems of Organisms
 leukocyte: blood and lymphatics, immune system; **ocular**
 surface: sensory system, inflammation; **tear**: sensory system,
 film instability

IT Diseases
keratoconjunctivitis sicca: eye disease, etiology,
dry eye
Keratoconjunctivitis Sicca (MeSH)

IT Chemicals & Biochemicals
 ICAM-1 [intercellular adhesion molecule-1]: expression; IL-1
 [interleukin-1]; TNF-alpha [tumor necrosis factor-alpha]; **c-**
Jun N-terminal kinase [EC
 2.7.1.112]: activation; matrix metalloproteinase-9

IT Miscellaneous Descriptors
 chronic inflammation

RN 155215-87-5 (**c-Jun N-terminal**
kinase)
 80449-02-1 (**c-Jun N-terminal**
kinase)
 155215-87-5 (EC 2.7.1.112)
 80449-02-1 (EC 2.7.1.112)
 146480-36-6 (matrix metalloproteinase-9)

L640 ANSWER 72 OF 79 TOXCENTER COPYRIGHT 2005 ACS on STN
 ACCESSION NUMBER: 2004:151485 TOXCENTER
 DOCUMENT NUMBER: RISKLINE-2004030002
 TITLE: Safety Assessment of Salicylic Acid, Butyloctyl
 Salicylate, Calcium Salicylate, C12-15 Alkyl Salicylate,
 Capryloyl Salicylic Acid, Hexyldodecyl Salicylate,
 Isocetyl Salicylate, Isodecyl Salicylate, Magnesium
 Salicylate, MEA-Salicylate.....
 AUTHOR(S): Anonymous
 SOURCE: Int J Toxicol, (2003) 22 Suppl 3 108 p.
 FILE SEGMENT: RISKLINE
 LANGUAGE: English
 ENTRY DATE: Entered STN: 20040713
 Last Updated on STN: 20050803

ED Entered STN: 20040713
 Last Updated on STN: 20050803

AB Salicylic Acid is an aromatic acid used in cosmetic formulations as a
 denaturant, a hair conditioning agent, and a skin-conditioning
 agent-miscellaneous. The Calcium, Magnesium, and MEA salts are used as
 preservatives. Potassium Salicylate is used as a cosmetic biocide and
 preservative. Sodium Salicylate is used as a denaturant and preservative.
 The TEA salt of Salicylic Acid is used as a UV light absorber. Several
 Salicylic Acid esters are used as skin-conditioning agents-miscellaneous
 (Capryloyl, C12-15 Alkyl, Isocetyl, Isodecyl, and Tridecyl). Butyloctyl

Salicylate and Hexyldodecyl Salicylate are used as pair-conditioning agents and skin-conditioning agents-miscellaneous. Ethylhexyl Salicylate (formerly known as Octyl Salicylate) is used as a fragrance ingredient, sunscreen agent, and UV light absorber, and Methyl Salicylate is used as a denaturant and flavoring agent. Myristyl Salicylate has no re-ported function. Salicylic Acid and Methyl Salicylate are soluble in organic solvents, but only slightly soluble in water. Ethylhexyl Salicylate is not soluble in water. Calcium, Potassium, and Sodium Salicylate are soluble in water. Potassium Salicylate is reported to be very soluble in water and alcohol. These ingredients have either no odor or only a faint odor, except for Methyl Salicylate, which has the characteristic odor of wintergreen. Consistent with the several medical treatments involving salicylates, test methodologies have been developed for detecting Salicylic Acid in urine and serum. Heavy metal concentration limitations are described for USP grade Magnesium, Sodium, and Methyl Salicylates and for cosmetic grade Methyl Salicylate. Salicylic Acid and Ethylhexyl Salicylate absorb UVB radiation. Salicylic Acid is used in 107 cosmetic formulations at concentrations ranging from 0.0008% to 3%. Ethylhexyl Salicylate is used in 87 formulations at 0.001% to 8%. Methyl Salicylate is used in 25 formulations at 0.0001% to 0.6%. Sodium Salicylate is used in seven formulations at 0.09% to 2%. TEA-Salicylate is used in five formulations at 0.0001% to 0.75%. Capryloyl Salicylate is used in five formulations at 0.1% to 1%. Isodecyl Salicylate is used in three formulations, but no concentration of use information was reported. Isocetyl Salicylate is not re-ported to FDA as used, but is reported to CTFA as being used at concentrations ranging from 3% to 5%. Likewise, Butyloctyl Salicylate is not reported to FDA as being used, but is reported to CTFA as being used at 0.5% to 5%. Methyl Salicylate is used in perfumery. Salicylic Acid, Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium Salicylate, and TEA-Salicylate are allowed for use in cosmetics in the European Union as preservatives at a maximum concentration of 5% (acid), except that these ingredients are not to be used in preparations for children under 3 years of age, except for shampoo formulations, which must bear a label warning against use on children under 3 years of age. In Japan, Salicylic Acid which conforms to the standards of the Japanese Standards of Cosmetic Ingredients (JSCI) has precedent for use at a maximum concentration of 0.2% in all categories except eyeliner preparations, in which it is not used. Sodium Salicylate which conforms to the specifications of the JSCI has precedent for use at a maximum concentration (calculated as total Salicylic Acid) of 1% in cleansing preparations and of 0.2% in hair care, treatment, makeup, fragrance, sun-tan and sunscreen, and nail makeup preparations; it is not used in eyeliner, lip, oral, or bath preparations. Sodium Salicylate is restricted as to the percent as total Salicylic Acid salts al-lowed in a formulation. Methyl Salicylate, which conforms to the specifications of the JSCI, has precedent for use at a maximum concentration of 0.1% in all Comprehensive Licensing Standards of Cosmetics (CLS) categories except eyeliner preparations, in which it is not used. Ethylhexyl Salicylate, which conforms to the specifications of the Japanese Cosmetic Ingredient Codex, has precedent at a maximum concentration of 10% in suntan/sunscreen preparations and of 1% in all other CLS preparations except eyeliner and bath preparations, in which it is not used. Methyl and Ethylhexyl Salicylates are restricted in that the total percentage of UV absorbers in a formulation shall not exceed 10%. These ingredients have uses in foods and drugs that are regulated by FDA. Salicylic Acid, Magnesium Salicylate, Sodium Salicylate, and Methyl Salicylate have FDA-specified uses as indirect food additives. Salicylic Acid is an approved active ingredient for use in topical OTC acne drug products at concentrations of 0.5% to 2%; in OTC wart remover drug products at concentrations of 12% to 40% in a plaster vehicle, 5% to 17%

in a collodion-like vehicle, and 15% in a karaya gum, glycol plaster vehicle with proper labeling directions; in corn and callus remover OTC drug products at concentrations of 12% to 40% in a plaster vehicle and 12% to 17.6% in a collodion-like vehicle with proper labeling directions; and in OTC drugs for the control of dandruff, seborrheic dermatitis, and psoriasis at a concentration of 1.8% to 3%. Salicylic Acid has been present in OTC topical acne preparations (at concentrations of 2% to 5%), external analgesics and skin protectants used for poison ivy, oak, and sumac, and topical antifungal drug products. Calcium Salicylate has been present in OTC internal analgesic drug products. Sodium Salicylate has been present in OTC dandruff/seborrheic dermatitis/psoriasis and digestive aid drug products. TEA-Salicylate has been present in OTC external analgesic-fever blister and cold sore; insect bite and sting; and poison ivy, oak, and sumac drug products. Methyl Salicylate has been present in OTC smoking deterrent drugs, boil treatment, dandruff/seborrheic dermatitis/psoriasis, fever blister and cold sore treatment, oral health care, and skin protectant-astringent drug products. However, currently FDA has concluded that there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for these specified OTC uses. Any drug product intended to be taken orally that contains any salicylate ingredient, except effervescent preparations, must bear a statement warning to keep the product out of the reach of children. Any drug containing >5% Methyl Salicylate must bear a label that warns that misdirected use may be dangerous and that the product should be kept out of the reach of children. TEA-Salicylate is allowed for use as an active ingredient in sunscreens at concentrations of < 12%, whereas Ethylhexyl Salicylate is allowed at concentrations of <5%. In veterinary practice, Salicylic Acid is allowed for use in the removal of scar tissue from the teat canal of milk-producing cows; however, a residue tolerance of 0 has been established for milk from dairy animals. In clinical practice, Salicylic Acid has been used in the treatment of ichthyosiform dermatoses. A traditional use of Methyl Salicylate is as a counterirritant. Salicylic Acid is used in the manufacture of aspirin. Salicylic Acid is also used in the manufacture of salicylates and resins and as a dyestuff intermediate, prevulcanization inhibitor, analytical reagent, and fungicide. Sodium Salicylate is used as a preservative for paste, mucilage, glues, and hides. Absorption of salicylates from the stomach is normally rapid. Extensive data are available in animals and humans from oral delivery studies. Metabolism by hepatic microsomal enzyme systems conjugates salicylates to glycine, forms glucuronides, or oxidizes them to hydroxybenzoic acids. Salicylates are also absorbed percutaneously. Urinary metabolites resulting from per-cutaneous delivery are reportedly quantitatively different from those seen with oral delivery, with more glucuronides found and more unmetabolized Salicylic Acid. Data on percutaneous absorption are available from in vitro and in vivo testing of penetration through animal skin. In vitro data are available for pig, mouse, and rat skin. In vivo percutaneous absorption data are available for rabbits, guinea pigs, rats, mice (including hairless mice), dogs, and monkeys. Data describing penetration through human skin are also available. These animal and human data describe the following percutaneous absorption patterns: rate of penetration is proportional to concentration applied; absorption is dependent on the vehicle (e.g., ethanol > water); absorption varies as a function of pH; and absorption is greater through damaged skin compared to normal skin. Around 10% of applied salicylates can remain in the skin. Parenteral absorption data are also available. Salicylic Acid is **keratolytic**. Salicylic Acid is reported to enhance percutaneous penetration of vitamin A, ammoniated mercury, and triamcinolone acetonide, but not methyl nicotinate (which itself rapidly penetrates skin), hydrocortisone, diflucortolone-21-valerate, or cyclosporine. One study describes the

minimal inhibitory concentrations of Salicylic Acid against bacteria, yeasts, and fungi, asserting that its preservative action is restricted to the pH range 2 to 5. Other data show that Salicylic acid inhibits growth of the following cells in culture: HeLa, human prostatic carcinoma, dog distal renal tubular, pig renal proximal tubular, rat kidney, human hepatoma, *B. subtilis*, and *E. coli*. Sodium Salicylate inhibits growth of human fibroblast and rat hepatoma cells in culture at high doses. Inhibition of iNOS is one hypothesis for the cytotoxicity of Sodium Salicylate in several mammalian cell lines. Methyl Salicylate inhibited HeLa and *B. subtilis* cell growth in culture. Salicylic Acid has anti-inflammatory effects. Sodium Salicylate influences interferon titres in mice; interferes with neutrophil function in vitro; inhibits induction of chemokine mRNA and activation of NF-KB in bone marrow cells; inhibits TNF-induced activation of c-Jun N-terminal kinase and c-fos mRNA in human diploid fibroblasts; and enhances tyrosine phosphorylation and increases p38 kinase activity in COS cells. Methyl Salicylate produced an inflammatory response in the ear of female mice, but in vitro exposure of human epidermal keratinocytes to Methyl Salicylate failed to induce IL-8, TNF-alpha, or GM-CSF. Salicylic acid produces pharmacologic/physiologic effects as follows: increases the stability of lysosomal membranes in rats and decreases ALT activity in the medium of cultured rat hepatocytes. Sodium Salicylate influenced blood pH in rats, and markedly increased bile flow in rats dosed intraperitoneally, but few other hepatic changes were seen. Little acute toxicity (LD50 in rats; >2 g/kg) via a dermal exposure route is seen for Salicylic Acid, Methyl Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. These compare with oral acute LD50 values for Salicylic Acid in rats ranging from a low of 0.891 g/kg to a high of 1.58 g/kg; for Sodium Salicylate, between 0.9 g/kg and 1.7 g/kg; for Isodecyl Salicylate, no toxicity at levels as high as 4.83 g/kg; for Methyl Salicylate, between 0.887 g/kg and 1.25 g/kg; for Ethylhexyl (Octyl) Salicylate, >2 g/kg; for Tridecyl Salicylate, >1.98 g/kg; and for Butyloctyl Salicylate, >5 g/kg. Values for acute oral toxicity in other species are consistent with these values. Methyl Salicylate given by inhalation is not lethal in mice and rats. The parenteral LD50 for Salicylic Acid in mice is 0.52 g/kg and the acute toxicity of Sodium Salicylate Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, and Tridecyl Salicylate via this route of administration are generally in the one gram per kilogram range. Short-term oral, inhalation, and parenteral exposures to Methyl Salicylate are available. Inconsistent results are seen regarding bone lesions with oral exposures, but reduced growth and feed consumption are consistently seen. No toxicity is seen with inhalation of Methyl Salicylate in a series of 20 exposures of 7 h each at 0.7 g/m³ and no bone lesions were seen with parenteral exposure. Sodium Salicylate oral exposures are linked with reduced growth and feed consumption, clear kidney damage, and some liver damage; parenteral exposures result in hyperpnea and profuse diuresis in single animal experiments. Salicylic Acid oral delivery produces liver and plasma enzyme changes. Subchronic dermal, oral, and inhalation studies are available for Methyl Salicylate. Dermal and inhalation exposures are associated with kidney damage. Inhalation exposures also produce pulmonary focal hemorrhages and hyperplasia. Oral exposure results in reduced weight gain and bone lesions that disappear if Methyl Salicylate is coadministered with Calcium Carbonate. No toxicity is seen with oral subchronic exposure to Isodecyl Salicylate or Tridecyl Salicylate. Oral subchronic exposure to Sodium Salicylate is associated with reduced growth and feed consumption, and indication of some bone lesions and isolated muscle weakness. Chronic exposure data are available for Methyl Salicylate. Adverse effects are seen as a function of the level of exposure in 2-year rat studies, with 2% producing bone lesions

and 0.7% not doing so. Liver damage is seen in dogs exposed to 0.15 g/kg/day in one study, kidney and liver weight increases in another study at the same exposure, but no liver or kidney abnormalities in a study at 0.167 g/kg/day. Dermal irritation studies are available for Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. Application of 500 mg (in 0.5 ml) of Isodecyl, Tridecyl, and Butyloctyl Salicylate are not irritating. Undiluted application of Ethylhexyl (Octyl) Salicylate produces minimal to mild irritation. Methyl Salicylate at concentrations of greater than 50% is clearly irritating. One study of the effect of vehicle on Methyl Salicylate irritation shows irritation at concentrations as low as 1 % with a 70% ethanol vehicle producing the most irritation and polyethylene glycol producing little or no irritation at Methyl Salicylate concentrations up to 6%. The ocular irritation potential is negative for Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate. Data are available on the use of a local lymph node assay to determine the sensitization potential of Salicylic Acid and Methyl Salicylate. Although Salicylic Acid at a concentration of 20% in acetone is positive in this assay, a concentration of 20% in acetone/olive oil is not. Methyl Salicylate is negative at concentrations up to 25 %, independent of vehicle. Maximization tests of Methyl Salicylate are negative, as they are for Ethylhexyl (Octyl) Salicylate and Butyloctyl Salicylate. Neither Salicylic Acid nor Tridecyl Salicylate are photosensitizers. Salicylic Acid, produced when aspirin is rapidly hydrolyzed to Salicylic Acid after absorption from the gut, was reported to be the causative agent in aspirin teratogenesis in animals. Dermal exposures to Methyl Salicylate, oral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate, and parenteral exposures to Salicylic Acid, Sodium Salicylate, and Methyl Salicylate are all associated with reproductive and developmental toxicity as a function of blood levels reached as a result of exposure. An exposure assessment of a representative cosmetic product used on a daily basis is available which estimates that the exposure from the cosmetic product would be only 20% of the level seen with ingestion of a "baby" aspirin (81 mg) on a daily basis. This exposure assessment further contends that the reproductive and developmental toxicity from the daily use of a baby aspirin is not significant. Studies of the genotoxic potential of Salicylic Acid, Sodium Salicylate, Isodecyl Salicylate, Methyl Salicylate, Ethylhexyl (Octyl) Salicylate, Tridecyl Salicylate, and Butyloctyl Salicylate are negative, except that Salicylic Acid is positive in a B. subtilis rec assay (negative in seven other bacterial tests and one mammalian test); Methyl Salicylate is positive in S. typhimurium strains TA98 and TA100 with metabolic activation (negative in two other Ames tests); and Sodium Salicylate is positive in an in vivo chromosome aberration study in mice (negative SCE in vivo in mice, and in four in vitro test systems). Methyl Salicylate, in a mouse skin painting study, does not induce neoplasms. Likewise, Methyl Salicylate is negative in a mouse pulmonary tumor system. In vitro predictors of carcinogenesis are also negative for Salicylic Acid and Sodium Salicylate. Clinical tests for cumulative irritation are available for the following ingredients at the specified concentrations: Salicylic Acid (2%-minimal cumulative irritation; 1.5 %-slight or no irritation); TEA-Salicylate (8%-no irritation); Methyl Salicylate (>12%-pain and erythema; 8%-no irritation; 1% aerosol-erythema); Ethylhexyl (Octyl) Salicylate (4%-no irritation); and Tridecyl Salicylate (no irritation). In 20 patients with eczema or contact dermatitis, Methyl Salicylate at 67% is reported to cause irritation in 8 subjects; at 40%, 2 subjects; and at 38%, 15%, and 3.75%-no irritation in any subject. If Salicylic Acid is applied after the application of agents (benzoic acid, cinnamic aldehyde, methyl nicotinate, and DMSO) known to cause nonimmunologic immediate contact

reactions in the skin, the erythema induced by benzoic acid, cinnamic aldehyde, and methyl nicotinate is reduced, but there is no effect on edema. In normal skin, Salicylic Acid, Methyl Salicylate, and Ethyl-hexyl (Octyl) Salicylate are not sensitizers. In patients with venous leg eczema, Salicylic Acid augments histidine release in 3/320 challenged with ragweed pollen. Sodium Salicylate injected in the skin of aspirin intolerant individuals affected several parameters as follows: 1/23 had a positive skin test to Sodium Salicylate; 2/31 were positive in the passive cutaneous anaphalaxis test; and 2/26 were positive in the lymphocyte transformation test. Salicylic Acid is not a photosensitizer, nor is it phototoxic. Salicylic Acid and Ethylhexyl (Octyl) Salicylate are low level photoprotective agents. Salicylic Acid exacerbates urticarial reactions to aspirin; 13 of 18 patients in one study and 6 of 20 in another. At 5% in petrolatum, however, Salicylic Acid does not cause any urticarial reactions in atopic, urticarial, nonatopic, and nonallergic patients.

Salicylic Acid is well-documented to have **keratolytic** action on normal human skin. It had a small therapeutic effect in patients with various forms of ichthyosiform dermatoses, but decreased clearing in 8 of 11 psoriasis patients when compared to UV therapy alone. Therapeutic toxicities include nausea, vomiting, tinnitus, dizziness, headache, dullness, confusion, sweating, rapid pulse and breathing, skin eruptions, and fever. One estimate is that a blood concentration >300 ug/ml of a salicylate should be considered toxic. Toxic reactions occur more frequently in children. Care must be taken in prescribing salicylate-containing medications because systemic clearance of salicylates may be reduced with age. Severe poisoning can result in delirium, hallucinations, convulsions, coma, and respiratory or cardiovascular collapse. Reversible hearing loss and tinnitus is a reported side effect of salicylates at therapeutic levels. Methyl S

AB alicylate taken in quantities greater than or equal to 1 teaspoon are reported to be quite toxic (equivalent of the salicylate that could be derived from 20+ adult aspirin tablets). Accidental poisoning is not uncommon, especially in children; symptoms of poisoning include kidney irritation, vomiting, and convulsions. The average lethal dose of Methyl Salicylate is 10 ml for children and 30 ml for adults. Use of topical analgesics with Methyl Salicylate in combination with oral warfarin can result in adverse reactions. Numerous case studies report toxic reactions to oral ingestion of salicylates. Dermal toxicity is also described in the case literature as follows: dermal application of Salicylic Acid with concomitant oral administration of a nonsteroidal anti-inflammatory drug; following dermal application of a Salicylic Acid ointment in an elderly subject recovering from acute renal failure; topical application of Methyl Salicylate (and menthol) followed by the application of heat (skin and muscle necrosis and interstitial nephritis); and severe urticaria and angioedema with Methyl Salicylate exposure. In two case studies of reactions to a wart paint containing Salicylic Acid, Salicylic Acid (tested at 3% in petrolatum) was not the causative agent. Two percent Methyl Salicylate in arachis oil and 2% aqueous Sodium Salicylate produced positive patch test results in a patient with acute dermatitis who had been using an ointment containing menthol, camphor. Twelve percent Methyl Salicylate and 5% Salicylic Acid in yellow soft paraffin produced positive patch tests in four patients with dermatitis and one with psoriasis, all with some history of exposure to salicylates. A review of radiographs taken in 155 cases of juvenile arthritis in which various forms of salicylates had been administered at concentrations ranging from 0.1 to 3.24 g for several months did not find any evidence of bone lesions. Conclusion. Based on the available information, the CIR Expert Panel concluded that Salicylic Acid, the salts Calcium Salicylate, Magnesium Salicylate, MEA-Salicylate, Potassium Salicylate, Sodium

Salicylate, and TEA-Salicylate; the esters Capryloyl Salicylic Acid, C12-15 Alkyl Salicylate, Isocetyl Salicylate, Isodecyl Salicylate, Methyl Salicylate, Myristyl Salicylate, Ethylhexyl Salicylate; and Tridecyl Salicylate, and the compounds Butyloctyl Salicylate and Hexyldodecyl Salicylate are safe as used when formulated to avoid skin irritation and when formulated to avoid increasing the skin's sun sensitivity, or, when increased sun sensitivity would be expected, directions for use include the daily use of sun protection.

ST Miscellaneous Descriptors

ANIMAL; acute toxicity; subacute toxicity; subchronic toxicity; chronic toxicity; irritancy; hypersensitivity; carcinogenicity; genetic toxicity; reproductive and developmental tests; teratogens; embryo-fetal toxicity; toxicokinetics; blood; liver; urinary tract; nervous system; dose effect; dose response; HUMAN; case report; human exposure; irritancy; hypersensitivity; toxicokinetics; skin; cosmetics; risk assessment; dose effect

RN 69-72-7; 824-35-1; 18917-89-0; 59866-70-5; 578-36-9; 54-21-7; 2174-16-5; 118-60-5; 119-36-8; 19666-17-2; 19666-16-1;

L640 ANSWER 73 OF 79 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-41037 DRUGU B P V

TITLE: Possible involvement of p44/p42 MAP kinase in retinoic acid-stimulated vascular endothelial growth factor release in aortic smooth muscle cells.

AUTHOR: Tanabe K; Hirade K; Ishisaki A; Shu E; Suga H; Kitajima Y; Katagiri Y; Dohi S; Kozawa O

CORPORATE SOURCE: Univ.Gifu

LOCATION: Gifu, Jap.

SOURCE: Atherosclerosis (175, No. 2, 245-51, 2004) 6 Fig. 1 Tab. 35 Ref.

CODEN: ATHSBL ISSN: 0021-9150

AVAIL. OF DOC.: Department of Pharmacology, Gifu University Graduate School of Medicine, Gifu 501-1194, Japan. (O.K.). (e-mail: okozawa@cc.gifu-u.ac.jp).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB PD-98059 and U-0126 (both Calbiochem-Novabiochem) dose-dependently suppressed all-trans retinoic acid (RA, tretinoin, Sigma-Chemical)-induced vascular endothelial growth factor (VEGF) release and phosphorylation of p44/p42 mitogen-activated protein kinase (MAPK) in A10 cells derived from fetal rat aortic smooth muscles. RA inhibited the increase of A10 cell number. RA had little effect on the phosphorylation of p38 MAP kinase or stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK). Actinomycin D (Nacalai-Tesque) also reduced RA-induced VEGF release. Data suggest that RA stimulates VEGF release in a p44/p42 MAPK-dependent manner in aortic smooth muscle cells.

L640 ANSWER 74 OF 79 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN

ACCESSION NUMBER: 2005-02899 DRUGU P V

TITLE: Retinoic acid inhibits growth of immortalized and weakly tumorigenic human breast epithelial cells (HBEC), but not highly tumorigenic HBEC: Molecular mechanisms of loss of anti-proliferative effect of retinoic acid during breast carcinogenesis.

AUTHOR: Eun Hyun Ahn; Chia Cheng Chang; Talmage D A

CORPORATE SOURCE: Univ.Columbia; Univ.Michigan-State

LOCATION: Columbia, NY; East Lansing, MI, USA

SOURCE: Proc.Am.Assoc.Cancer Res. (95 Meet., 199, 2004) ISSN:
0197-016X
AVAIL. OF DOC.: Columbia University, New York, NY, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The inhibitory effect of retinoic acid on tumor growth is attenuated as tumors develop to more advanced stages. The mechanism of loss of anti-tumorigenic action of retinoic acid is not well understood. This study investigated the anti-proliferative effect of all-trans retinoic acid (RA) during breast carcinogenesis using a novel cell culture system of human breast epithelial cells (HBEC). Loss of anti-proliferative effect might be associated with a stage of breast cells overexpressing neu oncogene which might interfere with the ability of RA to regulate cell signaling kinases and cell cycle regulating proteins. (conference abstract: 95th Annual Meeting of the American Association for Cancer Research, Orlando, Florida, USA, March 27-31, 2004).

L640 ANSWER 75 OF 79 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-07416 DRUGU B P V S
TITLE: Induction of apoptosis in retinoid-refractory acute myelogenous leukemia by a novel AHPN analog.
AUTHOR: Zhang Y; Dawson M I; Ning Y; Polin L; Parchment R E; Corbett T; Mohamed A N; Feng K C; Farhana L; Fontana J A
CORPORATE SOURCE: Univ.Wayne-State; Mol.Med.Res.Inst.Mountain-View; Univ.British-Columbia; Univ.Oregon-State; Univ.New-Mexico
LOCATION: USA; Can.
SOURCE: Blood (102, No. 10, 3743-52, 2003) 9 Fig. 3 Tab. 79 Ref.
CODEN: BLOOAW ISSN: 0006-4971
AVAIL. OF DOC.: John D Dingell VA Medical Center, Oncology 11M-HO, 4646 John R St, Detroit, MI 48201, U.S.A. (J.A.F., 22 authors).
(e-mail: joseph.fontana@med.va.gov).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB (E)-4-(3-(1-adamantyl)-4-hydroxyphenyl)-3-chlorocinnamic acid (3-Cl-AHPC), but not trans-retinoic acid (tretinoin, tRA), inhibited proliferation and induced cell death in human acute megakaryocytic M07e, KG-1, HL-60R acute myelogenous leukemia (AML) cells in-vitro. 3-Cl-AHPC blocked leukemic cell and CFU-granulocyte/macrophage (GM) formation. PD-169316 and SP-600125, but not PD-98059 (all 3 Calbiochem), inhibited both p38 and **c-Jun N-terminal kinase** (JNK) activation. I.v. 3-Cl-AHPC and i.v. 6-(3-(1-adamantyl)-4-hydroxyphenyl)-2-naphthalenecarboxylic acid (AHPN/CD437) induced weight loss in mice in-vivo. 3-Cl-AHPC prolonged survival duration in i.v. murine AML 1498 tumor-bearing mice. Data suggest that 3-Cl-AHPC is a potent inducer of apoptosis in AML cells and may represent a novel therapy in the treatment of this disease.

L640 ANSWER 76 OF 79 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-31053 DRUGU P B S V
TITLE: Retinoic acid differentially regulates cancer cell proliferation via dose-dependent modulation of the mitogen-activated protein kinase pathway.
AUTHOR: Crowe D L; Kim R; Chandraratna R A S
CORPORATE SOURCE: Univ.Southern-California; Allergan
LOCATION: Los Angeles; Irvine, Cal., USA
SOURCE: Molecular Cancer Research (1, No. 7, 532-40, 2003) 7 Fig. 42

Ref. ISSN: 1541-7786
AVAIL. OF DOC.: Center for Craniofacial Molecular Biology, University of
Southern California, 2250 Alcazar Street, Los Angeles, CA
90033, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Tretinoin (RA) is used to treat some tumors, but when given in diet to
smokers lung cancer was increased. In-vitro studies with human squamous
cell carcinoma lines (SCC) showed low dose RA induced proliferation via
increased epidermal growth factor (EGF) signaling, while high dose RA
inhibited proliferation by reducing ERK1 activation.

L640 ANSWER 77 OF 79 DRUGU COPYRIGHT 2005 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-17485 DRUGU P B
TITLE: Salicylic acid reverses phorbol 12-myristate-13-acetate
(PMA)- and tumor necrosis factor alpha (TNF-alpha)-induced
insulin receptor substrate 1 (IRS1) serine 307
phosphorylation and insulin resistance in human embryonic
kidney 293 (HEK293) cells.
AUTHOR: Jiang G; Dallas Yang Q; Liu F; Moller D E; Zhang B B
CORPORATE SOURCE: Merck-USA
LOCATION: Rahway, N.J., USA
SOURCE: J.Biol.Chem. (278, No. 1, 180-86, 2003) 7 Fig. 52 Ref.
CODEN: JBCHA3 ISSN: 0021-9258
AVAIL. OF DOC.: Metabolic Disorders-Diabetes, Merck Research Laboratories,
RY80N-C31, PO Box 2000, Rahway, NJ 07065, U.S.A. (B.B.Z.).
(e-mail: bei_zhang@merck.com).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The effects of salicylic acid (SA) on PMA- and TNF-alpha-induced insulin
(INS) (all Sigma-Chemical) resistance in human embryonic kidney 293 cells
stably expressing INS receptor substrate 1 (IRS1) (HEK293.IRS1 cells)
were investigated in-vitro. PMA and TNF-alpha inhibited INS-induced Akt
phosphorylation and promoted IRS1 phosphorylation on Ser-307.
Pretreatment with SA reversed the effects of PMA and TNF-alpha on Akt and
Ser-307. PMA, but not TNF-alpha, activated protein kinase C (PKC)
isoforms and IKKbeta. PMA and TNF-alpha activated c-Jun
N-terminal kinase (JNK). SP-600125 prevented
PMA and TNF-alpha-induced IRS1 Ser-307 phosphorylation. SA inhibited JNK
activation induced by PMA and TNF-alpha. These findings suggest that SA
can reverse the inhibitory effects of TNF-alpha on INS signaling via an
IKKbeta-independent mechanism, potentially involving the inhibition of
JNK activation.

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STN
ACCESSION NUMBER: 2005:637385 SCISEARCH
THE GENUINE ARTICLE: 911CZ
TITLE: UVB reduces cornified envelope proteins and barrier
function through transglutaminase and c-
Jun N-terminal kinase
pathways in human corneal epithelial cells
AUTHOR: Tong L M (Reprint); Corrales R; Chen Z; de Paiva C S; Li D
Q; Pflugfelder S C
SOURCE: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (2005) Vol.
46, Supp. [S]. MA 2112.

ISSN: 0146-0404.
PUBLISHER: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK
PARKWAY, ROCKVILLE, MD 20852-1606 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 29 Jun 2005
Last Updated on STN: 29 Jun 2005
ED Entered STN: 29 Jun 2005
Last Updated on STN: 29 Jun 2005

L640 ANSWER 79 OF 79 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on
STN

ACCESSION NUMBER: 2003:999274 SCISEARCH
THE GENUINE ARTICLE: 709CK
TITLE: Role of the **c-Jun N-terminal kinase** (JNK) in the
corneal epithelial wound healing
AUTHOR: Okada Y (Reprint); Saika S; Shirai K; Miyamoto T; Yamanaka
O; Ohnishi Y
CORPORATE SOURCE: Wakayama Med Univ, Dept Ophthalmol, Wakayama, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, (MAY 2003)
Vol. 44, Supp. [2], pp. U330-U330. MA 3838.
ISSN: 0146-0404.
PUBLISHER: ASSOC RESEARCH VISION OPHTHALMOLOGY INC, 12300 TWINBROOK
PARKWAY, ROCKVILLE, MD 20852-1606 USA.
DOCUMENT TYPE: Conference; Journal
LANGUAGE: English
REFERENCE COUNT: 0
ENTRY DATE: Entered STN: 8 Dec 2003
Last Updated on STN: 8 Dec 2003
ED Entered STN: 8 Dec 2003
Last Updated on STN: 8 Dec 2003

=> file stnguide

FILE 'STNGUIDE' ENTERED AT 08:04:24 ON 29 SEP 2005
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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Sep 23, 2005 (20050923/UP).

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=> d que 132

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L6      3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7      1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L8      SEL PLU=ON L6 1- CHEM : 11 TERMS
L9      432 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L10     186 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
L11     SEL PLU=ON L7 1- CHEM : 13 TERMS
L12     4144 SEA FILE=HCAPLUS ABB=ON PLU=ON L11
L13     931 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L15     35883 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
L16     21166 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
,NT/CT
L17     17731 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
PFT,NT/CT
L18     610 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
CT
L19     3 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) AND (L15 OR L16
OR L17 OR L18)
L20     27 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) AND (L15 OR L16
OR L17 OR L18)
L25     QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L26     1 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) (L) L25
L27     24 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) (L) L25
L28     47 SEA FILE=HCAPLUS ABB=ON PLU=ON L19 OR L20 OR L26 OR L27
L29     65 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10 OR L12 OR L13) AND
L25
L30     68 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29)
L31     5 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND (L9 OR L10)
L32     3 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND (AY<2003 OR PY<2003
OR PRY<2003)

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=> d que 133

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L6      3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7      1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L8      SEL PLU=ON L6 1- CHEM : 11 TERMS
L9      432 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L10     186 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
L11     SEL PLU=ON L7 1- CHEM : 13 TERMS
L12     4144 SEA FILE=HCAPLUS ABB=ON PLU=ON L11
L13     931 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L15     35883 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
L16     21166 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
,NT/CT
L17     17731 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
PFT,NT/CT
L18     610 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
CT
L19     3 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) AND (L15 OR L16
OR L17 OR L18)
L20     27 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) AND (L15 OR L16
OR L17 OR L18)
L25     QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L26     1 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) (L) L25

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L27 24 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) (L) L25
 L28 47 SEA FILE=HCAPLUS ABB=ON PLU=ON L19 OR L20 OR L26 OR L27
 L29 65 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10 OR L12 OR L13) AND
 L25
 L30 68 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29)
 L31 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND (L9 OR L10)
 L32 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 AND (AY<2003 OR PY<2003
 OR PRY<2003)
 L33 2 SEA FILE=HCAPLUS ABB=ON PLU=ON L31 NOT L32

=> d que 135

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L8 SEL PLU=ON L6 1- CHEM : 11 TERMS
 L9 432 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
 L10 186 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
 L11 SEL PLU=ON L7 1- CHEM : 13 TERMS
 L12 4144 SEA FILE=HCAPLUS ABB=ON PLU=ON L11
 L13 931 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
 L15 35883 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L16 21166 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
 ,NT/CT
 L17 17731 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
 PFT,NT/CT
 L18 610 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
 CT
 L19 3 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) AND (L15 OR L16
 OR L17 OR L18)
 L20 27 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) AND (L15 OR L16
 OR L17 OR L18)
 L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRIMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L26 1 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) (L) L25
 L27 24 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) (L) L25
 L28 47 SEA FILE=HCAPLUS ABB=ON PLU=ON L19 OR L20 OR L26 OR L27
 L29 65 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10 OR L12 OR L13) AND
 L25
 L30 68 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29)
 L31 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND (L9 OR L10)
 L34 63 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 NOT L31
 L35 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 AND (AY<2003 OR PY<2003
 OR PRY<2003)

=> d que 136

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L8 SEL PLU=ON L6 1- CHEM : 11 TERMS
 L9 432 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
 L10 186 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
 L11 SEL PLU=ON L7 1- CHEM : 13 TERMS
 L12 4144 SEA FILE=HCAPLUS ABB=ON PLU=ON L11
 L13 931 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
 L15 35883 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L16 21166 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
 ,NT/CT
 L17 17731 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+

PFT,NT/CT

L18 610 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
CT

L19 3 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) AND (L15 OR L16
OR L17 OR L18)

L20 27 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) AND (L15 OR L16
OR L17 OR L18)

L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L26 1 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10) (L) L25

L27 24 SEA FILE=HCAPLUS ABB=ON PLU=ON (L12 OR L13) (L) L25

L28 47 SEA FILE=HCAPLUS ABB=ON PLU=ON L19 OR L20 OR L26 OR L27

L29 65 SEA FILE=HCAPLUS ABB=ON PLU=ON (L9 OR L10 OR L12 OR L13) AND
L25

L30 68 SEA FILE=HCAPLUS ABB=ON PLU=ON (L28 OR L29)

L31 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND (L9 OR L10)

L34 63 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 NOT L31

L35 31 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 AND (AY<2003 OR PY<2003
OR PRY<2003)

L36 32 SEA FILE=HCAPLUS ABB=ON PLU=ON L34 NOT L35

=> d his 143

(FILE 'USPATFULL, USPAT2' ENTERED AT 14:26:50 ON 28 SEP 2005)

L43 8 S L42 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d que 143

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN

L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L38 21 SEA L6

L39 8 SEA L38 AND L25/TI,IT,BI,ST,CC

L40 9 SEA A61P027-02/IPC

L41 0 SEA L38 AND L40

L42 8 SEA L39 OR L41

L43 8 SEA L42 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d his 151

(FILE 'USPATFULL, USPAT2' ENTERED AT 14:26:50 ON 28 SEP 2005)

L51 24 S L50 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d que 151

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN

L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN

L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L38 21 SEA L6

L39 8 SEA L38 AND L25/TI,IT,BI,ST,CC

L40 9 SEA A61P027-02/IPC

L41 0 SEA L38 AND L40

L42 8 SEA L39 OR L41

L43 8 SEA L42 AND (AY<2003 OR PY<2003 OR PRY<2003)
 L44 64 SEA L7
 L48 30 SEA L44 AND L25/TI, IT, BI, ST, CC
 L50 29 SEA L48 NOT L43
 L51 24 SEA L50 AND (AY<2003 OR PY<2003 OR PRY<2003)

=> d his 152

(FILE 'USPATFULL, USPAT2' ENTERED AT 14:26:50 ON 28 SEP 2005)

L52 5 S L50 NOT L51

=> d que 152

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN, CRN
 L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN, CRN
 L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L38 21 SEA L6
 L39 8 SEA L38 AND L25/TI, IT, BI, ST, CC
 L40 9 SEA A61P027-02/IPC
 L41 0 SEA L38 AND L40
 L42 8 SEA L39 OR L41
 L43 8 SEA L42 AND (AY<2003 OR PY<2003 OR PRY<2003)
 L44 64 SEA L7
 L48 30 SEA L44 AND L25/TI, IT, BI, ST, CC
 L50 29 SEA L48 NOT L43
 L51 24 SEA L50 AND (AY<2003 OR PY<2003 OR PRY<2003)
 L52 5 SEA L50 NOT L51

=> d que 168

L53 8 SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR
 RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
 L55 8 SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0, M1, M2, M3, M4, M5, M6
 L56 8 SEA FILE=WPIX ABB=ON PLU=ON L53 OR L55
 L57 3915 SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L58 16334 SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03
 OR B12-J08 OR C12-J08 OR E12-J08)/MC
 L59 1 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (L57 OR L58)
 L60 3 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L61 8 SEA FILE=WPIX ABB=ON PLU=ON L56 OR L59 OR L60
 L62 819 SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
 L63 115 SEA FILE=WPIX ABB=ON PLU=ON L62 AND (L57 OR L58)
 L64 105 SEA FILE=WPIX ABB=ON PLU=ON L63 AND (EYE/BIX OR EYES/BIX OR
 OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX
 OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR
 ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR
 LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTH
 AL?/BIX)
 L65 28 SEA FILE=WPIX ABB=ON PLU=ON L64 AND ((DRY?(3A)EYE?) OR
 ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR
 ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN?

OR ?XEROPH?)/BIX

L66 35 SEA FILE=WPIX ABB=ON PLU=ON L61 OR L65

L67 28 SEA FILE=WPIX ABB=ON PLU=ON L66 AND (AY<2003 OR PY<2003 OR PRY<2003)

L68 5 SEA FILE=WPIX ABB=ON PLU=ON L67 AND L61

=> d que 169

L53 8 SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)

L55 8 SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6

L56 8 SEA FILE=WPIX ABB=ON PLU=ON L53 OR L55

L57 3915 SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC

L58 16334 SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR B12-J08 OR C12-J08 OR E12-J08)/MC

L59 1 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (L57 OR L58)

L60 3 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L61 8 SEA FILE=WPIX ABB=ON PLU=ON L56 OR L59 OR L60

L62 819 SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BIX OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))

L63 115 SEA FILE=WPIX ABB=ON PLU=ON L62 AND (L57 OR L58)

L64 105 SEA FILE=WPIX ABB=ON PLU=ON L63 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L65 28 SEA FILE=WPIX ABB=ON PLU=ON L64 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROPH?)/BIX

L66 35 SEA FILE=WPIX ABB=ON PLU=ON L61 OR L65

L67 28 SEA FILE=WPIX ABB=ON PLU=ON L66 AND (AY<2003 OR PY<2003 OR PRY<2003)

L68 5 SEA FILE=WPIX ABB=ON PLU=ON L67 AND L61

L69 3 SEA FILE=WPIX ABB=ON PLU=ON L61 NOT L68

=> d que 170

L53 8 SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)

L55 8 SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6

L56 8 SEA FILE=WPIX ABB=ON PLU=ON L53 OR L55

L57 3915 SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC

L58 16334 SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR B12-J08 OR C12-J08 OR E12-J08)/MC

L59 1 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (L57 OR L58)

L60 3 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L61 8 SEA FILE=WPIX ABB=ON PLU=ON L56 OR L59 OR L60

L62 819 SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BIX

X OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))

L63 115 SEA FILE=WPIX ABB=ON PLU=ON L62 AND (L57 OR L58)

L64 105 SEA FILE=WPIX ABB=ON PLU=ON L63 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L65 28 SEA FILE=WPIX ABB=ON PLU=ON L64 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROPH?)/BIX)

L66 35 SEA FILE=WPIX ABB=ON PLU=ON L61 OR L65

L67 28 SEA FILE=WPIX ABB=ON PLU=ON L66 AND (AY<2003 OR PY<2003 OR PRY<2003)

L70 24 SEA FILE=WPIX ABB=ON PLU=ON L67 AND L65

=> d que 171

L53 8 SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA8XOT-K/DCN OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)

L55 8 SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6

L56 8 SEA FILE=WPIX ABB=ON PLU=ON L53 OR L55

L57 3915 SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC

L58 16334 SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR B12-J08 OR C12-J08 OR E12-J08)/MC

L59 1 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (L57 OR L58)

L60 3 SEA FILE=WPIX ABB=ON PLU=ON L56 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L61 8 SEA FILE=WPIX ABB=ON PLU=ON L56 OR L59 OR L60

L62 819 SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BIX OR ((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))

L63 115 SEA FILE=WPIX ABB=ON PLU=ON L62 AND (L57 OR L58)

L64 105 SEA FILE=WPIX ABB=ON PLU=ON L63 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITIS?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR ?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)

L65 28 SEA FILE=WPIX ABB=ON PLU=ON L64 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROPH?)/BIX)

L66 35 SEA FILE=WPIX ABB=ON PLU=ON L61 OR L65

L67 28 SEA FILE=WPIX ABB=ON PLU=ON L66 AND (AY<2003 OR PY<2003 OR PRY<2003)

L70 24 SEA FILE=WPIX ABB=ON PLU=ON L67 AND L65

L71 11 SEA FILE=WPIX ABB=ON PLU=ON L66 NOT L70

=> d que 176

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN

L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L72 SEL PLU=ON L6 1- CHEM : 11 TERMS
 L73 218 SEA FILE=MEDLINE ABB=ON PLU=ON L72
 L76 1 SEA FILE=MEDLINE ABB=ON PLU=ON L73 AND L25

=> d que 182

L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L74 9127 SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
 L77 SEL PLU=ON L7 1- CHEM : 13 TERMS
 L78 3278 SEA FILE=MEDLINE ABB=ON PLU=ON L77
 L79 2 SEA FILE=MEDLINE ABB=ON PLU=ON L78 AND L74
 L80 32 SEA FILE=MEDLINE ABB=ON PLU=ON L78 AND L25
 L81 32 SEA FILE=MEDLINE ABB=ON PLU=ON (L79 OR L80)
 L82 11 SEA FILE=MEDLINE ABB=ON PLU=ON L81 AND PY<2003

=> d que 183

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L72 SEL PLU=ON L6 1- CHEM : 11 TERMS
 L73 218 SEA FILE=MEDLINE ABB=ON PLU=ON L72
 L74 9127 SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
 L76 1 SEA FILE=MEDLINE ABB=ON PLU=ON L73 AND L25
 L77 SEL PLU=ON L7 1- CHEM : 13 TERMS
 L78 3278 SEA FILE=MEDLINE ABB=ON PLU=ON L77
 L79 2 SEA FILE=MEDLINE ABB=ON PLU=ON L78 AND L74
 L80 32 SEA FILE=MEDLINE ABB=ON PLU=ON L78 AND L25
 L81 32 SEA FILE=MEDLINE ABB=ON PLU=ON (L79 OR L80)
 L82 11 SEA FILE=MEDLINE ABB=ON PLU=ON L81 AND PY<2003
 L83 20 SEA FILE=MEDLINE ABB=ON PLU=ON L81 NOT (L82 OR L76)

=> d que 191

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
 R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
 CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L84 SEL PLU=ON L6 1- CHEM : 11 TERMS
 L85 547 SEA FILE=EMBASE ABB=ON PLU=ON L84
 L86 2325 SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
 L87 0 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L86
 L88 1 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L25
 L89 1 SEA FILE=EMBASE ABB=ON PLU=ON (L87 OR L88)
 L90 0 SEA FILE=EMBASE ABB=ON PLU=ON L89 AND (PY<2003 OR MY<2003)
 L91 1 SEA FILE=EMBASE ABB=ON PLU=ON L89 NOT L90

=> d que 198

L6 3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN

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L7          1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L25         QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L84         SEL PLU=ON L6 1- CHEM : 11 TERMS
L85         547 SEA FILE=EMBASE ABB=ON PLU=ON L84
L86         2325 SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
L87         0 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L86
L88         1 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L25
L89         1 SEA FILE=EMBASE ABB=ON PLU=ON (L87 OR L88)
L90         0 SEA FILE=EMBASE ABB=ON PLU=ON L89 AND (PY<2003 OR MY<2003)
L91         1 SEA FILE=EMBASE ABB=ON PLU=ON L89 NOT L90
L92         SEL PLU=ON L7 1- CHEM : 13 TERMS
L93         2867 SEA FILE=EMBASE ABB=ON PLU=ON L92
L94         2 SEA FILE=EMBASE ABB=ON PLU=ON L93 AND L86
L95         24 SEA FILE=EMBASE ABB=ON PLU=ON L93 AND L25
L96         24 SEA FILE=EMBASE ABB=ON PLU=ON (L94 OR L95)
L97         24 SEA FILE=EMBASE ABB=ON PLU=ON L96 NOT L91
L98         8 SEA FILE=EMBASE ABB=ON PLU=ON L97 AND (PY<2003 OR MY<2003)

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=> d que 199

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L6          3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7          1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L25         QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L84         SEL PLU=ON L6 1- CHEM : 11 TERMS
L85         547 SEA FILE=EMBASE ABB=ON PLU=ON L84
L86         2325 SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
L87         0 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L86
L88         1 SEA FILE=EMBASE ABB=ON PLU=ON L85 AND L25
L89         1 SEA FILE=EMBASE ABB=ON PLU=ON (L87 OR L88)
L90         0 SEA FILE=EMBASE ABB=ON PLU=ON L89 AND (PY<2003 OR MY<2003)
L91         1 SEA FILE=EMBASE ABB=ON PLU=ON L89 NOT L90
L92         SEL PLU=ON L7 1- CHEM : 13 TERMS
L93         2867 SEA FILE=EMBASE ABB=ON PLU=ON L92
L94         2 SEA FILE=EMBASE ABB=ON PLU=ON L93 AND L86
L95         24 SEA FILE=EMBASE ABB=ON PLU=ON L93 AND L25
L96         24 SEA FILE=EMBASE ABB=ON PLU=ON (L94 OR L95)
L97         24 SEA FILE=EMBASE ABB=ON PLU=ON L96 NOT L91
L98         8 SEA FILE=EMBASE ABB=ON PLU=ON L97 AND (PY<2003 OR MY<2003)
L99         16 SEA FILE=EMBASE ABB=ON PLU=ON L97 NOT L98

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=> d his 1111

(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH' ENTERED AT 15:24:51 ON 28 SEP 2005)

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L111        1 S L110 AND L103

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=> d que 1111

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L6          3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7          1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L25         QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
           R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
           ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
           CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

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L100      SEL  PLU=ON  L6 1- CHEM :      11 TERMS
L101      813 SEA L100
L102      6 SEA L101 AND L25
L103      6 DUP REM L102 (0 DUPLICATES REMOVED)
L104      SEL  PLU=ON  L7 1- CHEM :      13 TERMS
L105      13886 SEA L104
L106      139 SEA L105 AND L25
L107      88 DUP REM L106 (51 DUPLICATES REMOVED)
L108      44 SEA L107 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
          LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
          ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L109      48 SEA L103 OR L108
L110      18 SEA L109 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L111      1 SEA L110 AND L103

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=> d his l112

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          (FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
          VETU, VETB, SCISEARCH' ENTERED AT 15:24:51 ON 28 SEP 2005)
L112      5 S L103 NOT L111

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=> d que l112

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L6        3 SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L7        1 SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L25      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
          R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
          ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
          CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L100      SEL  PLU=ON  L6 1- CHEM :      11 TERMS
L101      813 SEA L100
L102      6 SEA L101 AND L25
L103      6 DUP REM L102 (0 DUPLICATES REMOVED)
L104      SEL  PLU=ON  L7 1- CHEM :      13 TERMS
L105      13886 SEA L104
L106      139 SEA L105 AND L25
L107      88 DUP REM L106 (51 DUPLICATES REMOVED)
L108      44 SEA L107 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
          LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
          ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L109      48 SEA L103 OR L108
L110      18 SEA L109 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L111      1 SEA L110 AND L103
L112      5 SEA L103 NOT L111

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=> d his l113

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          (FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
          VETU, VETB, SCISEARCH' ENTERED AT 15:24:51 ON 28 SEP 2005)
L113      17 S L110 AND L108

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=> d que l113

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L6        3 SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L7        1 SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L25      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
          R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
          ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
          CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L100      SEL  PLU=ON  L6 1- CHEM :      11 TERMS

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L101      813 SEA L100
L102      6 SEA L101 AND L25
L103      6 DUP REM L102 (0 DUPLICATES REMOVED)
L104      SEL PLU=ON L7 1- CHEM :      13 TERMS
L105      13886 SEA L104
L106      139 SEA L105 AND L25
L107      88 DUP REM L106 (51 DUPLICATES REMOVED)
L108      44 SEA L107 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
        LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
        ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L109      48 SEA L103 OR L108
L110      18 SEA L109 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L113      17 SEA L110 AND L108

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=> d his l114

(FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
VETU, VETB, SCISEARCH' ENTERED AT 15:24:51 ON 28 SEP 2005)

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L114      27 S L108 NOT L113

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=> d que l114

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L6        3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7        1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L25       QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? O
        R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
        ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
        CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L100      SEL PLU=ON L6 1- CHEM :      11 TERMS
L101      813 SEA L100
L102      6 SEA L101 AND L25
L103      6 DUP REM L102 (0 DUPLICATES REMOVED)
L104      SEL PLU=ON L7 1- CHEM :      13 TERMS
L105      13886 SEA L104
L106      139 SEA L105 AND L25
L107      88 DUP REM L106 (51 DUPLICATES REMOVED)
L108      44 SEA L107 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR
        LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO? OR ?KERATECT
        ? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L109      48 SEA L103 OR L108
L110      18 SEA L109 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L113      17 SEA L110 AND L108
L114      27 SEA L108 NOT L113

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=> d que l124

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L6        3 SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L7        1 SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L8        SEL PLU=ON L6 1- CHEM :      11 TERMS
L9        432 SEA FILE=HCAPLUS ABB=ON PLU=ON L8
L10       186 SEA FILE=HCAPLUS ABB=ON PLU=ON L6
L11       SEL PLU=ON L7 1- CHEM :      13 TERMS
L12       4144 SEA FILE=HCAPLUS ABB=ON PLU=ON L11
L13       931 SEA FILE=HCAPLUS ABB=ON PLU=ON L7
L15       35883 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
L16       21166 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
        ,NT/CT
L17       17731 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
        PFT,NT/CT
L18       610 SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/

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CT
L19      3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L9 OR L10) AND (L15 OR L16
OR L17 OR L18)
L20     27 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L12 OR L13) AND (L15 OR L16
OR L17 OR L18)
L25      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L26      1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L9 OR L10) (L) L25
L27     24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L12 OR L13) (L) L25
L28     47 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19 OR L20 OR L26 OR L27
L29     65 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L9 OR L10 OR L12 OR L13) AND
L25
L30     68 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L28 OR L29)
L31      5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L30 AND (L9 OR L10)
L32      3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 AND (AY<2003 OR PY<2003
OR PRY<2003)
L33      2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 NOT L32
L115     37 SEA FILE=HCAPLUS ABB=ON  PLU=ON  129-56-6P? OR 129-56-6D?
L116      1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L115 AND (L15 OR L16 OR L17
OR L18)
L117      1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L115 AND L25
L118      1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L116 OR L117)
L119      0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L118 NOT (L32 OR L33)
L120     30 SEA FILE=HCAPLUS ABB=ON  PLU=ON  289898-51-7P? OR 289898-51-7D?

L121      0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND (L15 OR L16 OR L17
OR L18)
L122      0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L120 AND L25
L123      0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L121 OR L122)
L124      0 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L119 OR L123

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=> d his l137

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(FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS,
LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS'
ENTERED AT 15:45:07 ON 28 SEP 2005)

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L137      1 S L132 OR L135 OR L136
          SAVE TEMP L137 AUD006MULINV/A

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FILE 'STNGUIDE' ENTERED AT 15:55:02 ON 28 SEP 2005

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=> d que l137

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L6      3 SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L25      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? O
R ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LA
CHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L37      QUE ABB=ON  PLU=ON  JNK OR JNK1 OR P46JNK OR ((MITOGEN O
R JUN) (5A) ?KINAS?)
L125     323 SEA GAMACHE, D?/AU
L127      SEL ABB=ON  PLU=ON  L6 1- CHEM :      11 TERMS
L128     1874 SEA L127
L129     193 SEA L125 AND (L128 OR L37 OR L25)
L130      72 DUP REM L129 (121 DUPLICATES REMOVED)
L131      72 SEA L130 AND (L128 OR L129)
L132      1 SEA L130 AND (L128 OR L37)
L133     66 SEA L131 AND ALCON/PA,CS,SO

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L134 66 SEA L133 AND L25
L135 1 SEA L131 AND L128
L136 1 SEA L134 AND L128
L137 1 SEA L132 OR L135 OR L136

=> d his ful

(FILE 'HOME' ENTERED AT 12:24:55 ON 28 SEP 2005)

FILE 'STNGUIDE' ENTERED AT 12:25:06 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 12:25:20 ON 28 SEP 2005
L1 1 SEA ABB=ON PLU=ON US2003-650006/APPS
SAVE TEMP L1 AUD006HCAAPP/A

FILE 'STNGUIDE' ENTERED AT 12:25:45 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 12:25:57 ON 28 SEP 2005
D IBIB ED AB IND

FILE 'STNGUIDE' ENTERED AT 12:25:57 ON 28 SEP 2005

FILE 'WPIX' ENTERED AT 12:27:28 ON 28 SEP 2005
L2 1 SEA ABB=ON PLU=ON US2003-650006/APPS
SAVE TEMP L2 AUD006WPIAPP/A

FILE 'STNGUIDE' ENTERED AT 12:27:45 ON 28 SEP 2005

FILE 'WPIX' ENTERED AT 12:27:56 ON 28 SEP 2005
D IALL CMC PLE

FILE 'STNGUIDE' ENTERED AT 12:27:58 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 12:28:59 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 12:29:03 ON 28 SEP 2005
L3 TRA L1 1- RN : 13 TERMS

FILE 'REGISTRY' ENTERED AT 12:29:05 ON 28 SEP 2005
L4 13 SEA ABB=ON PLU=ON L3
SAVE TEMP L4 AUD006REGAPP/A
D SCAN

FILE 'STNGUIDE' ENTERED AT 12:29:35 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 12:32:09 ON 28 SEP 2005
L5 1 SEA ABB=ON PLU=ON L4 AND C14H8N2O/MF
D SCAN

L6 3 SEA ABB=ON PLU=ON 129-56-6/RN,CRN
D SCAN
SAVE TEMP L6 AUD006ANTH/A

L7 1 SEA ABB=ON PLU=ON 289898-51-7/RN,CRN
SAVE TEMP L7 AUD006CJUN/A

FILE 'STNGUIDE' ENTERED AT 12:34:59 ON 28 SEP 2005
D SAVED

FILE 'HCAPLUS' ENTERED AT 12:35:52 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 12:35:54 ON 28 SEP 2005

FILE 'STNGUIDE' ENTERED AT 12:35:56 ON 28 SEP 2005
D QUE L5

FILE 'REGISTRY' ENTERED AT 12:36:07 ON 28 SEP 2005
D IDE L5

FILE 'STNGUIDE' ENTERED AT 12:36:07 ON 28 SEP 2005
D QUE L7

FILE 'REGISTRY' ENTERED AT 12:36:30 ON 28 SEP 2005
D IDE L7

FILE 'STNGUIDE' ENTERED AT 12:36:30 ON 28 SEP 2005

FILE 'ZCAPLUS' ENTERED AT 13:03:44 ON 28 SEP 2005
E EYE, DISEASE/CT
E E3+ALL
E DRY EYE/CT
E E143+ALL

FILE 'HCAPLUS' ENTERED AT 13:06:13 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 13:06:18 ON 28 SEP 2005
SET SMARTSELECT ON
L8 SEL PLU=ON L6 1- CHEM : 11 TERMS
SET SMARTSELECT OFF

FILE 'HCAPLUS' ENTERED AT 13:06:19 ON 28 SEP 2005

L9 432 SEA ABB=ON PLU=ON L8
L10 186 SEA ABB=ON PLU=ON L6

FILE 'REGISTRY' ENTERED AT 13:06:44 ON 28 SEP 2005
SET SMARTSELECT ON
L11 SEL PLU=ON L7 1- CHEM : 13 TERMS
SET SMARTSELECT OFF

FILE 'HCAPLUS' ENTERED AT 13:06:44 ON 28 SEP 2005

L12 4144 SEA ABB=ON PLU=ON L11
L13 931 SEA ABB=ON PLU=ON L7

FILE 'STNGUIDE' ENTERED AT 13:07:14 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:13:00 ON 28 SEP 2005
L14 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACT? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LACHRYMA?
OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L15 35883 SEA ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
L16 21166 SEA ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT,NT/CT
L17 17731 SEA ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+PFT,NT/CT
L18 610 SEA ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/CT
L19 3 SEA ABB=ON PLU=ON (L9 OR L10) AND (L15 OR L16 OR L17 OR L18)

L20 27 SEA ABB=ON PLU=ON (L12 OR L13) AND (L15 OR L16 OR L17 OR
L18)

L21 1 SEA ABB=ON PLU=ON (L9 OR L10) (L) L14
L22 39 SEA ABB=ON PLU=ON (L12 OR L13) (L) L14
L23 62 SEA ABB=ON PLU=ON (L19 OR L20 OR L21 OR L22)

FILE 'STNGUIDE' ENTERED AT 13:16:28 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:18:02 ON 28 SEP 2005

L24 33 SEA ABB=ON PLU=ON L23 AND (AY<2003 OR PY<2003 OR PRY<2003)
 SAVE TEMP L24 AUD006HCA1B/A
 D SCAN TI HIT

FILE 'STNGUIDE' ENTERED AT 13:19:09 ON 28 SEP 2005

D QUE L14

FILE 'HCAPLUS' ENTERED AT 13:22:49 ON 28 SEP 2005

L25 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
 LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

FILE 'STNGUIDE' ENTERED AT 13:23:03 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:25:28 ON 28 SEP 2005

L26 1 SEA ABB=ON PLU=ON (L9 OR L10) (L) L25
L27 24 SEA ABB=ON PLU=ON (L12 OR L13) (L) L25
L28 47 SEA ABB=ON PLU=ON L19 OR L20 OR L26 OR L27
 D SCAN TI HIT

FILE 'STNGUIDE' ENTERED AT 13:26:59 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:29:40 ON 28 SEP 2005

L29 65 SEA ABB=ON PLU=ON (L9 OR L10 OR L12 OR L13) AND L25
L30 68 SEA ABB=ON PLU=ON (L28 OR L29)

FILE 'STNGUIDE' ENTERED AT 13:31:58 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:32:40 ON 28 SEP 2005

L31 5 SEA ABB=ON PLU=ON L30 AND (L9 OR L10)
L32 3 SEA ABB=ON PLU=ON L31 AND (AY<2003 OR PY<2003 OR PRY<2003)
 SAVE TEMP L32 AUD006HCA1B/A
L33 2 SEA ABB=ON PLU=ON L31 NOT L32
 SAVE TEMP L33 AUD006HCA1A/A

FILE 'STNGUIDE' ENTERED AT 13:33:53 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 13:34:20 ON 28 SEP 2005

L34 63 SEA ABB=ON PLU=ON L30 NOT L31
L35 31 SEA ABB=ON PLU=ON L34 AND (AY<2003 OR PY<2003 OR PRY<2003)
 SAVE TEMP L35 AUD006HCA2B/A
L36 32 SEA ABB=ON PLU=ON L34 NOT L35
 SAVE TEMP L36 AUD006HCA2A/A

FILE 'STNGUIDE' ENTERED AT 13:35:27 ON 28 SEP 2005

D SAVED

FILE 'HCAPLUS' ENTERED AT 14:22:52 ON 28 SEP 2005

L37 QUE ABB=ON PLU=ON JNK OR JNK1 OR P46JNK OR ((MITOGEN OR JUN)
 (5A) ?KINAS?)

FILE 'STNGUIDE' ENTERED AT 14:23:01 ON 28 SEP 2005

FILE 'USPATFULL, USPAT2' ENTERED AT 14:23:14 ON 28 SEP 2005

L38 21 SEA ABB=ON PLU=ON L6

L39 8 SEA ABB=ON PLU=ON L38 AND L25/TI,IT,BI,ST,CC
L40 9 SEA ABB=ON PLU=ON A61P027-02/IPC
L41 0 SEA ABB=ON PLU=ON L38 AND L40
L42 8 SEA ABB=ON PLU=ON L39 OR L41
D QUE
D KWIC 1-8

FILE 'STNGUIDE' ENTERED AT 14:25:39 ON 28 SEP 2005

FILE 'USPATFULL, USPAT2' ENTERED AT 14:26:50 ON 28 SEP 2005

L43 8 SEA ABB=ON PLU=ON L42 AND (AY<2003 OR PY<2003 OR PRY<2003)
SAVE TEMP L43 AUD006USP1B/A
L44 64 SEA ABB=ON PLU=ON L7
L45 5678 SEA ABB=ON PLU=ON L37/TI,BI,IT,ST,CC
D KWIC
L46 3235 SEA ABB=ON PLU=ON (L44 OR L45) AND L25/TI,IT,BI,ST,CC
L47 0 SEA ABB=ON PLU=ON L46 AND L40
L48 30 SEA ABB=ON PLU=ON L44 AND L25/TI,IT,BI,ST,CC
L49 30 SEA ABB=ON PLU=ON (L47 OR L48)
L50 29 SEA ABB=ON PLU=ON L48 NOT L43
L51 24 SEA ABB=ON PLU=ON L50 AND (AY<2003 OR PY<2003 OR PRY<2003)
SAVE TEMP L51 AUD006USP2B/A
L52 5 SEA ABB=ON PLU=ON L50 NOT L51
SAVE TEMP L52 AUD006USP2A/A

FILE 'STNGUIDE' ENTERED AT 14:30:43 ON 28 SEP 2005

D SAVED

FILE 'WPIX' ENTERED AT 14:31:45 ON 28 SEP 2005

E RA8XOT-K/DCN
L53 8 SEA ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA8XOT-K/DCN
OR RA8XOT-M/DCN OR RA8XOT-T/DCN OR RA8XOT-U/DCN)
D IDE
L54 0 SEA ABB=ON PLU=ON "L53"/M0,M1,M2,M3,M4,M5,M6
L55 8 SEA ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
L56 8 SEA ABB=ON PLU=ON L53 OR L55
D TRI 1-8

FILE 'STNGUIDE' ENTERED AT 14:35:17 ON 28 SEP 2005

FILE 'WPIX' ENTERED AT 14:35:47 ON 28 SEP 2005

L57 3915 SEA ABB=ON PLU=ON A61P027-02/IPC
L58 16334 SEA ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR B12-J08
OR C12-J08 OR E12-J08)/MC
L59 1 SEA ABB=ON PLU=ON L56 AND (L57 OR L58)
L60 3 SEA ABB=ON PLU=ON L56 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX
OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITI
S?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR
TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR
?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)
D TRI L60 1-3
L61 8 SEA ABB=ON PLU=ON L56 OR L59 OR L60
D TRI 1-8
SAVE TEMP L61 AUD006WPI1/A
L62 819 SEA ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BIX OR
((MITOGEN/BIX OR JUN/BIX) (5A) ?KINAS?/BIX))
L63 115 SEA ABB=ON PLU=ON L62 AND (L57 OR L58)
D TRI 1-5
L64 105 SEA ABB=ON PLU=ON L63 AND (EYE/BIX OR EYES/BIX OR OCULA?/BIX
OR ?OPHTHALM?/BIX OR ?OPHTHALM?/BIX OR ?KERATO?/BIX OR ?KERATITI

S?/BIX OR ?KERATECT?/BIX OR ?REFRACTI?/BIX OR ?CORNEA?/BIX OR
TEAR/BIX OR TEARS/BIX OR LACRIMA?/BIX OR LACHRYMA?/BIX OR
?CONJUNCTIV?/BIX OR ?SJOGREN?/BIX OR ?XEROPHTHAL?/BIX)
L65 28 SEA ABB=ON PLU=ON L64 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROPH?)/BIX
D TRI 1-28

FILE 'STNGUIDE' ENTERED AT 14:45:13 ON 28 SEP 2005

FILE 'WPIX' ENTERED AT 14:48:10 ON 28 SEP 2005

L66 35 SEA ABB=ON PLU=ON L61 OR L65
L67 28 SEA ABB=ON PLU=ON L66 AND (AY<2003 OR PY<2003 OR PRY<2003)
L68 5 SEA ABB=ON PLU=ON L67 AND L61
SAVE TEMP L68 AUD006WPI1B/A
L69 3 SEA ABB=ON PLU=ON L61 NOT L68
SAVE TEMP L69 AUD006WPI1A/A
L70 24 SEA ABB=ON PLU=ON L67 AND L65
SAVE TEMP L70 AUD006WPI2B/A
L71 11 SEA ABB=ON PLU=ON L66 NOT L70
SAVE TEMP L71 AUD006WPI2A/A

FILE 'STNGUIDE' ENTERED AT 15:06:05 ON 28 SEP 2005
D SAVED

FILE 'MEDLINE' ENTERED AT 15:07:07 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 15:07:13 ON 28 SEP 2005

SET SMARTSELECT ON
L72 SEL PLU=ON L6 1- CHEM : 11 TERMS
SET SMARTSELECT OFF

FILE 'MEDLINE' ENTERED AT 15:07:13 ON 28 SEP 2005

L73 218 SEA ABB=ON PLU=ON L72
L74 9127 SEA ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
L75 0 SEA ABB=ON PLU=ON L73 AND L74
L76 1 SEA ABB=ON PLU=ON L73 AND L25
D TRI 1
D BIB
SAVE TEMP L76 AUD006MED1A/A

FILE 'REGISTRY' ENTERED AT 15:09:07 ON 28 SEP 2005

SET SMARTSELECT ON
L77 SEL PLU=ON L7 1- CHEM : 13 TERMS
SET SMARTSELECT OFF

FILE 'MEDLINE' ENTERED AT 15:09:09 ON 28 SEP 2005

L78 3278 SEA ABB=ON PLU=ON L77
L79 2 SEA ABB=ON PLU=ON L78 AND L74
L80 32 SEA ABB=ON PLU=ON L78 AND L25
L81 32 SEA ABB=ON PLU=ON (L79 OR L80)
D TRI 1-32

FILE 'STNGUIDE' ENTERED AT 15:10:02 ON 28 SEP 2005

FILE 'MEDLINE' ENTERED AT 15:12:26 ON 28 SEP 2005

L82 11 SEA ABB=ON PLU=ON L81 AND PY<2003
SAVE TEMP L82 AUD006MED2B/A
L83 20 SEA ABB=ON PLU=ON L81 NOT (L82 OR L76)
SAVE TEMP L83 AUD006MED2A/A

FILE 'STNGUIDE' ENTERED AT 15:13:35 ON 28 SEP 2005
D SAVED

FILE 'EMBASE' ENTERED AT 15:14:49 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 15:14:55 ON 28 SEP 2005

L84 SET SMARTSELECT ON
SEL PLU=ON L6 1- CHEM : 11 TERMS
SET SMARTSELECT OFF

FILE 'EMBASE' ENTERED AT 15:14:55 ON 28 SEP 2005

L85 547 SEA ABB=ON PLU=ON L84
E DRY EYE/CT
E E171+ALL
E E169+ALL
L86 2325 SEA ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
L87 0 SEA ABB=ON PLU=ON L85 AND L86
L88 1 SEA ABB=ON PLU=ON L85 AND L25
L89 1 SEA ABB=ON PLU=ON (L87 OR L88)
D TRI
L90 0 SEA ABB=ON PLU=ON L89 AND (PY<2003 OR MY<2003)
L91 1 SEA ABB=ON PLU=ON L89 NOT L90
SAVE TEMP L91 AUD006EMB1A/A

FILE 'REGISTRY' ENTERED AT 15:17:40 ON 28 SEP 2005

L92 SET SMARTSELECT ON
SEL PLU=ON L7 1- CHEM : 13 TERMS
SET SMARTSELECT OFF

FILE 'EMBASE' ENTERED AT 15:17:41 ON 28 SEP 2005

L93 2867 SEA ABB=ON PLU=ON L92
L94 2 SEA ABB=ON PLU=ON L93 AND L86
L95 24 SEA ABB=ON PLU=ON L93 AND L25
L96 24 SEA ABB=ON PLU=ON (L94 OR L95)
L97 24 SEA ABB=ON PLU=ON L96 NOT L91
D TRI 1-4
L98 8 SEA ABB=ON PLU=ON L97 AND (PY<2003 OR MY<2003)
SAVE TEMP L98 AUD006EMB2B/A
L99 16 SEA ABB=ON PLU=ON L97 NOT L98
SAVE TEMP L99 AUD006EMB2A/A

FILE 'STNGUIDE' ENTERED AT 15:19:56 ON 28 SEP 2005
D SAVED

FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
VETU, VETB, SCISEARCH' ENTERED AT 15:22:43 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 15:22:50 ON 28 SEP 2005

L100 SET SMARTSELECT ON
SEL PLU=ON L6 1- CHEM : 11 TERMS
SET SMARTSELECT OFF

FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
VETU, VETB, SCISEARCH' ENTERED AT 15:22:51 ON 28 SEP 2005

L101 813 SEA ABB=ON PLU=ON L100
L102 6 SEA ABB=ON PLU=ON L101 AND L25
L103 6 DUP REM L102 (0 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE BIOSIS
ANSWERS '4-6' FROM FILE DRUGU

FILE 'REGISTRY' ENTERED AT 15:24:50 ON 28 SEP 2005

SET SMARTSELECT ON
L104 SEL PLU=ON L7 1- CHEM : 13 TERMS
SET SMARTSELECT OFF

FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH' ENTERED AT 15:24:51 ON 28 SEP 2005

L105 13886 SEA ABB=ON PLU=ON L104
L106 139 SEA ABB=ON PLU=ON L105 AND L25
L107 88 DUP REM L106 (51 DUPLICATES REMOVED)
ANSWERS '1-55' FROM FILE BIOSIS
ANSWERS '56-61' FROM FILE TOXCENTER
ANSWERS '62-69' FROM FILE PASCAL
ANSWER '70' FROM FILE CANCERLIT
ANSWERS '71-81' FROM FILE DRUGU
ANSWERS '82-88' FROM FILE SCISEARCH
D QUE L68
L108 44 SEA ABB=ON PLU=ON L107 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR
LACRIMA? OR LACHRYMA? OR TEAR OR TEARS OR ?CORNEA? OR ?KERATO?
OR ?KERATECT? OR ?KERATITIS? OR ?SJOGREN? OR ?XEROP?)
L109 48 SEA ABB=ON PLU=ON L103 OR L108
L110 18 SEA ABB=ON PLU=ON L109 AND (AY<2003 OR PY<2003 OR PRY<2003
OR MY<2003)
L111 1 SEA ABB=ON PLU=ON L110 AND L103
SAVE TEMP L111 AUD006MUL1B/A
L112 5 SEA ABB=ON PLU=ON L103 NOT L111
SAVE TEMP L112 AUD006MUL1A/A
L113 17 SEA ABB=ON PLU=ON L110 AND L108
SAVE TEMP L113 AUD006MUL2B/A
L114 27 SEA ABB=ON PLU=ON L108 NOT L113
SAVE TEMP L114 AUD006MUL2A/A
D SAVED

FILE 'STNGUIDE' ENTERED AT 15:37:09 ON 28 SEP 2005

FILE 'HCAPLUS' ENTERED AT 15:38:12 ON 28 SEP 2005

L115 37 SEA ABB=ON PLU=ON 129-56-6P? OR 129-56-6D?
L116 1 SEA ABB=ON PLU=ON L115 AND (L15 OR L16 OR L17 OR L18)
L117 1 SEA ABB=ON PLU=ON L115 AND L25
L118 1 SEA ABB=ON PLU=ON (L116 OR L117)
L119 0 SEA ABB=ON PLU=ON L118 NOT (L32 OR L33)
L120 30 SEA ABB=ON PLU=ON 289898-51-7P? OR 289898-51-7D?
L121 0 SEA ABB=ON PLU=ON L120 AND (L15 OR L16 OR L17 OR L18)
L122 0 SEA ABB=ON PLU=ON L120 AND L25
L123 0 SEA ABB=ON PLU=ON (L121 OR L122)
L124 0 SEA ABB=ON PLU=ON L119 OR L123
SAVE TEMP L124 AUD006HCANOT/A

FILE 'STNGUIDE' ENTERED AT 15:41:05 ON 28 SEP 2005

D SAVED

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS' ENTERED AT 15:42:38 ON 28 SEP 2005

L125 323 SEA ABB=ON PLU=ON GAMACHE, D?/AU

FILE 'REGISTRY' ENTERED AT 15:43:32 ON 28 SEP 2005

SET SMARTSELECT ON
L126 SEL PLU=ON L6 1- CHEM : 11 TERMS

SET SMARTSELECT OFF

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS,
LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS'
ENTERED AT 15:43:34 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 15:44:12 ON 28 SEP 2005
D IDE L5

FILE 'STNGUIDE' ENTERED AT 15:44:34 ON 28 SEP 2005

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS,
LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS'
ENTERED AT 15:44:46 ON 28 SEP 2005

FILE 'REGISTRY' ENTERED AT 15:45:06 ON 28 SEP 2005

SET SMARTSELECT ON
L127 SEL ABB=ON PLU=ON L6 1- CHEM : 11 TERMS
SET SMARTSELECT OFF

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, PASCAL, JICST-EPLUS,
LIFESCI, CANCERLIT, DRUGU, VETU, VETB, SCISEARCH, CONF, CONFSCI, DISSABS'
ENTERED AT 15:45:07 ON 28 SEP 2005

L128 1874 SEA ABB=ON PLU=ON L127
L129 193 SEA ABB=ON PLU=ON L125 AND (L128 OR L37 OR L25)
L130 72 DUP REM L129 (121 DUPLICATES REMOVED)
ANSWERS '1-45' FROM FILE HCAPLUS
ANSWERS '46-47' FROM FILE WPIX
ANSWERS '48-49' FROM FILE MEDLINE
ANSWERS '50-67' FROM FILE BIOSIS
ANSWERS '68-69' FROM FILE DRUGU
ANSWERS '70-72' FROM FILE SCISEARCH
L131 72 SEA ABB=ON PLU=ON L130 AND (L128 OR L129)
L132 1 SEA ABB=ON PLU=ON L130 AND (L128 OR L37)
L133 66 SEA ABB=ON PLU=ON L131 AND ALCON/PA,CS,SO
L134 66 SEA ABB=ON PLU=ON L133 AND L25
D QUE L132
D SCAN L132
D QUE L132
L135 1 SEA ABB=ON PLU=ON L131 AND L128
L136 1 SEA ABB=ON PLU=ON L134 AND L128
L137 1 SEA ABB=ON PLU=ON L132 OR L135 OR L136
SAVE TEMP L137 AUD006MULINV/A
D SAVED

FILE 'STNGUIDE' ENTERED AT 15:55:02 ON 28 SEP 2005

D QUE L32
D QUE L33
D QUE L35
D QUE L36
D QUE L43
D QUE L51
D QUE L52
D QUE L68
D QUE L69
D QUE L70
D QUE L71
D QUE L76
D QUE L82
D QUE L83

D QUE L91
D QUE L98
D QUE L99
D QUE L111
D QUE L112
D QUE L113
D QUE L114
D QUE L124
D QUE L137

FILE HOME

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Sep 23, 2005 (20050923/UP).

FILE HCAPLUS

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*
* The CA roles and document type information have been removed from *
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*

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FILE ZCAPLUS

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FILE COVERS 1907 - 28 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US6951031
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210555
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)

ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

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>>> USPAT2 is now available.  USPATFULL contains full text of the  <<<
>>> original, i.e., the earliest published granted patents or  <<<
>>> applications.  USPAT2 contains full text of the latest US  <<<
>>> publications, starting in 2001, for the inventions covered in  <<<
>>> USPATFULL.  A USPATFULL record contains not only the original  <<<
>>> published document but also a list of any subsequent  <<<
>>> publications.  The publication number, patent kind code, and  <<<
>>> publication date for all the US publications for an invention  <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL  <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc.  <<<

>>> USPATFULL and USPAT2 can be accessed and searched together  <<<
>>> through the new cluster USPATALL.  Type FILE USPATALL to  <<<
>>> enter this cluster.  <<<
>>>  <<<
>>> Use USPATALL when searching terms such as patent assignees,  <<<
>>> classifications, or claims, that may potentially change from  <<<
>>> the earliest to the latest publication.  <<<
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This file contains CAS Registry Numbers for easy and accurate
substance identification.

FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US2005202247
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210551
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text
of the latest US publications, starting in 2001, for the inventions
covered in USPATFULL. USPATFULL contains full text of the original
published US patents from 1971 to date and the original applications
from 2001. In addition, a USPATFULL record for an invention contains
a complete list of publications that may be searched in standard
search fields, e.g., /PN, /PK, etc.

USPATFULL and USPAT2 can be accessed and searched together through
the new cluster USPATALL. Type FILE USPATALL to enter this cluster.

Use USPATALL when searching terms such as patent assignees,
classifications, or claims, that may potentially change from the
earliest to the latest publication.

FILE MEDLINE

FILE LAST UPDATED: 27 SEP 2005 (20050927/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP
RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE

FILE COVERS 1974 TO 22 Sep 2005 (20050922/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS

FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNS) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 21 September 2005 (20050921/ED)

FILE RELOADED: 19 October 2003.

FILE TOXCENTER

FILE COVERS 1907 TO 27 Sep 2005 (20050927/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields.
See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

FILE PASCAL

FILE LAST UPDATED: 26 SEP 2005 <20050926/UP>

FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE
IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS

FILE COVERS 1985 TO 26 SEP 2005 (20050926/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE LIFESCI

FILE COVERS 1978 TO 19 Sep 2005 (20050919/ED)

FILE CANCERLIT

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE DRUGU

FILE LAST UPDATED: 27 SEP 2005 <20050927/UP>

>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<

>>> THESAURUS AVAILABLE IN /CT <<<

FILE VETU

FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>

FILE COVERS 1983-2001

FILE VETB

FILE LAST UPDATED: 25 SEP 94 <940925/UP>

FILE COVERS 1968-1982

FILE SCISEARCH

FILE COVERS 1974 TO 22 Sep 2005 (20050922/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE CONF

FILE LAST UPDATED: 23 SEP 2005 <20050923/UP>

FILE COVERS 1976 TO DATE.

FILE CONFSCI

FILE COVERS 1973 TO 25 May 2005 (20050525/ED)

FILE DISSABS

FILE COVERS 1861 TO 26 AUG 2005 (20050826/ED)

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=> => d his ful

(FILE 'HOME' ENTERED AT 07:38:49 ON 29 SEP 2005)

FILE 'HCAPLUS' ENTERED AT 07:38:58 ON 29 SEP 2005

ACT AUD006HCANOT/A

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L1 (      3)SEA ABB=ON  PLU=ON  129-56-6/RN,CRN
L2 (      1)SEA ABB=ON  PLU=ON  289898-51-7/RN,CRN
L3 (      SEL PLU=ON  L1 1-  CHEM :      11 TERMS
L4 (    432)SEA ABB=ON  PLU=ON  L3
L5 (    186)SEA ABB=ON  PLU=ON  L1
L6 (      SEL PLU=ON  L2 1-  CHEM :      13 TERMS
L7 (    4144)SEA ABB=ON  PLU=ON  L6
L8 (     931)SEA ABB=ON  PLU=ON  L2
L9 (   35883)SEA ABB=ON  PLU=ON  "EYE, DISEASE"+PFT,NT/CT
L10 (  21166)SEA ABB=ON  PLU=ON  "EYE, DISEASE OR DISORDER"+PFT,NT/CT
L11 ( 17731)SEA ABB=ON  PLU=ON  "EYES, DISEASES OR DISORDERS"+PFT,NT/CT
L12 (    610)SEA ABB=ON  PLU=ON  "EYE, DISEASE (L) DRY"+PFT,NT/CT
L13 (      3)SEA ABB=ON  PLU=ON  (L4 OR L5) AND (L9 OR L10 OR L11 OR L12)
L14 (     27)SEA ABB=ON  PLU=ON  (L7 OR L8) AND (L9 OR L10 OR L11 OR L12)
L15 (      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
      ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
      LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L16 (      1)SEA ABB=ON  PLU=ON  (L4 OR L5) (L) L15
L17 (     24)SEA ABB=ON  PLU=ON  (L7 OR L8) (L) L15
L18 (     47)SEA ABB=ON  PLU=ON  L13 OR L14 OR L16 OR L17
L19 (     65)SEA ABB=ON  PLU=ON  (L4 OR L5 OR L7 OR L8) AND L15
L20 (     68)SEA ABB=ON  PLU=ON  (L18 OR L19)
L21 (      5)SEA ABB=ON  PLU=ON  L20 AND (L4 OR L5)
L22 (      3)SEA ABB=ON  PLU=ON  L21 AND (AY<2003 OR PY<2003 OR PRY<2003)
L23 (      2)SEA ABB=ON  PLU=ON  L21 NOT L22
L24 (     37)SEA ABB=ON  PLU=ON  129-56-6P? OR 129-56-6D?
L25 (      1)SEA ABB=ON  PLU=ON  L24 AND (L9 OR L10 OR L11 OR L12)
L26 (      1)SEA ABB=ON  PLU=ON  L24 AND L15
L27 (      1)SEA ABB=ON  PLU=ON  (L25 OR L26)
L28 (      0)SEA ABB=ON  PLU=ON  L27 NOT (L22 OR L23)
L29 (     30)SEA ABB=ON  PLU=ON  289898-51-7P? OR 289898-51-7D?
L30 (      0)SEA ABB=ON  PLU=ON  L29 AND (L9 OR L10 OR L11 OR L12)
L31 (      0)SEA ABB=ON  PLU=ON  L29 AND L15
L32 (      0)SEA ABB=ON  PLU=ON  (L30 OR L31)
L33 (      0)SEA ABB=ON  PLU=ON  L28 OR L32
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ACT AUD006HCA1B/A

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L34 (      3)SEA ABB=ON  PLU=ON  129-56-6/RN,CRN
L35 (      1)SEA ABB=ON  PLU=ON  289898-51-7/RN,CRN
L36 (      SEL PLU=ON  L34 1-  CHEM :      11 TERMS
L37 (    432)SEA ABB=ON  PLU=ON  L36
L38 (    186)SEA ABB=ON  PLU=ON  L34
L39 (      SEL PLU=ON  L35 1-  CHEM :      13 TERMS
L40 (    4144)SEA ABB=ON  PLU=ON  L39
L41 (     931)SEA ABB=ON  PLU=ON  L35
L42 (   35883)SEA ABB=ON  PLU=ON  "EYE, DISEASE"+PFT,NT/CT
L43 (  21166)SEA ABB=ON  PLU=ON  "EYE, DISEASE OR DISORDER"+PFT,NT/CT
L44 ( 17731)SEA ABB=ON  PLU=ON  "EYES, DISEASES OR DISORDERS"+PFT,NT/CT
L45 (    610)SEA ABB=ON  PLU=ON  "EYE, DISEASE (L) DRY"+PFT,NT/CT
L46 (      3)SEA ABB=ON  PLU=ON  (L37 OR L38) AND (L42 OR L43 OR L44 OR
      L45)
L47 (     27)SEA ABB=ON  PLU=ON  (L40 OR L41) AND (L42 OR L43 OR L44 OR
      L45)
L48 (      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
      ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
      LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

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L49 (1)SEA ABB=ON PLU=ON (L37 OR L38) (L) L48
 L50 (24)SEA ABB=ON PLU=ON (L40 OR L41) (L) L48
 L51 (47)SEA ABB=ON PLU=ON L46 OR L47 OR L49 OR L50
 L52 (65)SEA ABB=ON PLU=ON (L37 OR L38 OR L40 OR L41) AND L48
 L53 (68)SEA ABB=ON PLU=ON (L51 OR L52)
 L54 (5)SEA ABB=ON PLU=ON L53 AND (L37 OR L38)
 L55 3 SEA ABB=ON PLU=ON L54 AND (AY<2003 OR PY<2003 OR PRY<2003)

 ACT AUD006HCA1A/A

L56 (3)SEA ABB=ON PLU=ON 129-56-6/RN,CRN
 L57 (1)SEA ABB=ON PLU=ON 289898-51-7/RN,CRN
 L58 SEL PLU=ON L56 1- CHEM : 11 TERMS
 L59 (432)SEA ABB=ON PLU=ON L58
 L60 (186)SEA ABB=ON PLU=ON L56
 L61 SEL PLU=ON L57 1- CHEM : 13 TERMS
 L62 (4144)SEA ABB=ON PLU=ON L61
 L63 (931)SEA ABB=ON PLU=ON L57
 L64 (35883)SEA ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L65 (21166)SEA ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT,NT/CT
 L66 (17731)SEA ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+PFT,NT/CT
 L67 (610)SEA ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/CT
 L68 (3)SEA ABB=ON PLU=ON (L59 OR L60) AND (L64 OR L65 OR L66 OR L67)
 L69 (27)SEA ABB=ON PLU=ON (L62 OR L63) AND (L64 OR L65 OR L66 OR L67)
 L70 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L71 (1)SEA ABB=ON PLU=ON (L59 OR L60) (L) L70
 L72 (24)SEA ABB=ON PLU=ON (L62 OR L63) (L) L70
 L73 (47)SEA ABB=ON PLU=ON L68 OR L69 OR L71 OR L72
 L74 (65)SEA ABB=ON PLU=ON (L59 OR L60 OR L62 OR L63) AND L70
 L75 (68)SEA ABB=ON PLU=ON (L73 OR L74)
 L76 (5)SEA ABB=ON PLU=ON L75 AND (L59 OR L60)
 L77 (3)SEA ABB=ON PLU=ON L76 AND (AY<2003 OR PY<2003 OR PRY<2003)
 L78 2 SEA ABB=ON PLU=ON L76 NOT L77

 ACT AUD006HCA2B/A

L79 (3)SEA ABB=ON PLU=ON 129-56-6/RN,CRN
 L80 (1)SEA ABB=ON PLU=ON 289898-51-7/RN,CRN
 L81 SEL PLU=ON L79 1- CHEM : 11 TERMS
 L82 (432)SEA ABB=ON PLU=ON L81
 L83 (186)SEA ABB=ON PLU=ON L79
 L84 SEL PLU=ON L80 1- CHEM : 13 TERMS
 L85 (4144)SEA ABB=ON PLU=ON L84
 L86 (931)SEA ABB=ON PLU=ON L80
 L87 (35883)SEA ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L88 (21166)SEA ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT,NT/CT
 L89 (17731)SEA ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+PFT,NT/CT
 L90 (610)SEA ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/CT
 L91 (3)SEA ABB=ON PLU=ON (L82 OR L83) AND (L87 OR L88 OR L89 OR L90)
 L92 (27)SEA ABB=ON PLU=ON (L85 OR L86) AND (L87 OR L88 OR L89 OR L90)
 L93 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR

LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L94 (1)SEA ABB=ON PLU=ON (L82 OR L83) (L) L93
 L95 (24)SEA ABB=ON PLU=ON (L85 OR L86) (L) L93
 L96 (47)SEA ABB=ON PLU=ON L91 OR L92 OR L94 OR L95
 L97 (65)SEA ABB=ON PLU=ON (L82 OR L83 OR L85 OR L86) AND L93
 L98 (68)SEA ABB=ON PLU=ON (L96 OR L97)
 L99 (5)SEA ABB=ON PLU=ON L98 AND (L82 OR L83)
 L100 (63)SEA FILE=HCAPLUS ABB=ON PLU=ON L98 NOT L99
 L101 31 SEA ABB=ON PLU=ON L100 AND (AY<2003 OR PY<2003 OR PRY<2003)

 ACT AUD006HCA2A/A

L102 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L103 (1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L104 SEL PLU=ON L102 1- CHEM : 11 TERMS
 L105 (432)SEA FILE=HCAPLUS ABB=ON PLU=ON L104
 L106 (186)SEA FILE=HCAPLUS ABB=ON PLU=ON L102
 L107 SEL PLU=ON L103 1- CHEM : 13 TERMS
 L108 (4144)SEA FILE=HCAPLUS ABB=ON PLU=ON L107
 L109 (931)SEA FILE=HCAPLUS ABB=ON PLU=ON L103
 L110 (35883)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE"+PFT,NT/CT
 L111 (21166)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE OR DISORDER"+PFT
 L112 (17731)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYES, DISEASES OR DISORDERS"+
 L113 (610)SEA FILE=HCAPLUS ABB=ON PLU=ON "EYE, DISEASE (L) DRY"+PFT,NT/
 L114 (3)SEA FILE=HCAPLUS ABB=ON PLU=ON (L105 OR L106) AND (L110 OR L1
 L115 (27)SEA FILE=HCAPLUS ABB=ON PLU=ON (L108 OR L109) AND (L110 OR L1
 L116 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
 LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?

L117 (1)SEA FILE=HCAPLUS ABB=ON PLU=ON (L105 OR L106) (L) L116
 L118 (24)SEA FILE=HCAPLUS ABB=ON PLU=ON (L108 OR L109) (L) L116
 L119 (47)SEA FILE=HCAPLUS ABB=ON PLU=ON L114 OR L115 OR L117 OR L118
 L120 (65)SEA FILE=HCAPLUS ABB=ON PLU=ON (L105 OR L106 OR L108 OR L109)
 L121 (68)SEA FILE=HCAPLUS ABB=ON PLU=ON (L119 OR L120)
 L122 (5)SEA FILE=HCAPLUS ABB=ON PLU=ON L121 AND (L105 OR L106)
 L123 (63)SEA FILE=HCAPLUS ABB=ON PLU=ON L121 NOT L122
 L124 (31)SEA FILE=HCAPLUS ABB=ON PLU=ON L123 AND (AY<2003 OR PY<2003 O
 L125 32 SEA ABB=ON PLU=ON L123 NOT L124

 FILE 'USPATFULL, USPAT2' ENTERED AT 07:40:05 ON 29 SEP 2005

ACT AUD006USP1B/A

L126 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 L127 (21)SEA L126
 L128 (8)SEA L127 AND L126/TI,IT,BI,ST,CC
 L129 (9)SEA A61P027-02/IPC
 L130 (0)SEA L127 AND L129
 L131 (8)SEA L128 OR L130
 L132 8 SEA ABB=ON PLU=ON L131 AND (AY<2003 OR PY<2003 OR PRY<2003)
 ACT AUD006USP2B/A

L133 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 L134 (21)SEA L133
 L135 (8)SEA L134 AND L133/TI,IT,BI,ST,CC
 L136 (9)SEA A61P027-02/IPC
 L137 (0)SEA L134 AND L136
 L138 (8)SEA L135 OR L137
 L139 (8)SEA L138 AND (AY<2003 OR PY<2003 OR PRY<2003)

L140(64)SEA L133
L141(30)SEA L140 AND L133/TI,IT,BI,ST,CC
L142(29)SEA L141 NOT L139
L143 24 SEA ABB=ON PLU=ON L142 AND (AY<2003 OR PY<2003 OR PRY<2003)

ACT AUD006USP2A/A

L144 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
L145(21)SEA L144
L146(8)SEA L145 AND L144/TI,IT,BI,ST,CC
L147(9)SEA A61P027-02/IPC
L148(0)SEA L145 AND L147
L149(8)SEA L146 OR L148
L150(8)SEA L149 AND (AY<2003 OR PY<2003 OR PRY<2003)
L151(64)SEA L144
L152(30)SEA L151 AND L144/TI,IT,BI,ST,CC
L153(29)SEA L152 NOT L150
L154(24)SEA L153 AND (AY<2003 OR PY<2003 OR PRY<2003)
L155 5 SEA ABB=ON PLU=ON L153 NOT L154

FILE 'WPIX' ENTERED AT 07:40:50 ON 29 SEP 2005

ACT AUD006WPI1B/A

L156(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA
L157(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
L158(8)SEA FILE=WPIX ABB=ON PLU=ON L156 OR L157
L159(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
L160(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR
L161(1)SEA FILE=WPIX ABB=ON PLU=ON L158 AND (L159 OR L160)
L162(3)SEA FILE=WPIX ABB=ON PLU=ON L158 AND (EYE/BIX OR EYES/BIX OR
L163(8)SEA FILE=WPIX ABB=ON PLU=ON L158 OR L161 OR L162
L164(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
L165(115)SEA FILE=WPIX ABB=ON PLU=ON L164 AND (L159 OR L160)
L166(105)SEA FILE=WPIX ABB=ON PLU=ON L165 AND (EYE/BIX OR EYES/BIX OR
L167(28)SEA FILE=WPIX ABB=ON PLU=ON L166 AND ((DRY?(3A)EYE?) OR ?REFR
L168(35)SEA FILE=WPIX ABB=ON PLU=ON L163 OR L167
L169(28)SEA FILE=WPIX ABB=ON PLU=ON L168 AND (AY<2003 OR PY<2003 OR P
L170 5 SEA ABB=ON PLU=ON L169 AND L163

ACT AUD006WPI1A/A

L171(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA
L172(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
L173(8)SEA FILE=WPIX ABB=ON PLU=ON L171 OR L172
L174(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
L175(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR
L176(1)SEA FILE=WPIX ABB=ON PLU=ON L173 AND (L174 OR L175)
L177(3)SEA FILE=WPIX ABB=ON PLU=ON L173 AND (EYE/BIX OR EYES/BIX OR
L178(8)SEA FILE=WPIX ABB=ON PLU=ON L173 OR L176 OR L177
L179(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
L180(115)SEA FILE=WPIX ABB=ON PLU=ON L179 AND (L174 OR L175)
L181(105)SEA FILE=WPIX ABB=ON PLU=ON L180 AND (EYE/BIX OR EYES/BIX OR
L182(28)SEA FILE=WPIX ABB=ON PLU=ON L181 AND ((DRY?(3A)EYE?) OR ?REFR
L183(35)SEA FILE=WPIX ABB=ON PLU=ON L178 OR L182
L184(28)SEA FILE=WPIX ABB=ON PLU=ON L183 AND (AY<2003 OR PY<2003 OR P
L185(5)SEA FILE=WPIX ABB=ON PLU=ON L184 AND L178
L186 3 SEA ABB=ON PLU=ON L178 NOT L185

ACT AUD006WPI2B/A

L187(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA
 L188(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
 L189(8)SEA FILE=WPIX ABB=ON PLU=ON L187 OR L188
 L190(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L191(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR
 L192(1)SEA FILE=WPIX ABB=ON PLU=ON L189 AND (L190 OR L191)
 L193(3)SEA FILE=WPIX ABB=ON PLU=ON L189 AND (EYE/BIX OR EYES/BIX OR
 L194(8)SEA FILE=WPIX ABB=ON PLU=ON L189 OR L192 OR L193
 L195(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 L196(115)SEA FILE=WPIX ABB=ON PLU=ON L195 AND (L190 OR L191)
 L197(105)SEA FILE=WPIX ABB=ON PLU=ON L196 AND (EYE/BIX OR EYES/BIX OR
 L198(28)SEA FILE=WPIX ABB=ON PLU=ON L197 AND ((DRY?(3A)EYE?) OR ?REFR
 L199(35)SEA FILE=WPIX ABB=ON PLU=ON L194 OR L198
 L200(28)SEA FILE=WPIX ABB=ON PLU=ON L199 AND (AY<2003 OR PY<2003 OR P
 L201 24 SEA ABB=ON PLU=ON L200 AND L198

 ACT AUD006WPI2A/A

L202(8)SEA FILE=WPIX ABB=ON PLU=ON (RA8XOT/DCN OR RA8XOT-D/DCN OR RA
 L203(8)SEA FILE=WPIX ABB=ON PLU=ON RA8XOT/M0,M1,M2,M3,M4,M5,M6
 L204(8)SEA FILE=WPIX ABB=ON PLU=ON L202 OR L203
 L205(3915)SEA FILE=WPIX ABB=ON PLU=ON A61P027-02/IPC
 L206(16334)SEA FILE=WPIX ABB=ON PLU=ON (B14-N03 OR C14-N03 OR E14-N03 OR
 L207(1)SEA FILE=WPIX ABB=ON PLU=ON L204 AND (L205 OR L206)
 L208(3)SEA FILE=WPIX ABB=ON PLU=ON L204 AND (EYE/BIX OR EYES/BIX OR
 L209(8)SEA FILE=WPIX ABB=ON PLU=ON L204 OR L207 OR L208
 L210(819)SEA FILE=WPIX ABB=ON PLU=ON (JNK/BIX OR JNK1/BIX OR P46JNK/BI
 L211(115)SEA FILE=WPIX ABB=ON PLU=ON L210 AND (L205 OR L206)
 L212(105)SEA FILE=WPIX ABB=ON PLU=ON L211 AND (EYE/BIX OR EYES/BIX OR
 L213(28)SEA FILE=WPIX ABB=ON PLU=ON L212 AND ((DRY?(3A)EYE?) OR ?REFR
 L214(35)SEA FILE=WPIX ABB=ON PLU=ON L209 OR L213
 L215(28)SEA FILE=WPIX ABB=ON PLU=ON L214 AND (AY<2003 OR PY<2003 OR P
 L216(24)SEA FILE=WPIX ABB=ON PLU=ON L215 AND L213
 L217 11 SEA ABB=ON PLU=ON L214 NOT L216

FILE 'MEDLINE' ENTERED AT 07:41:44 ON 29 SEP 2005

ACT AUD006MED1A/A

L218(3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
 L219 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
 LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L220 SEL PLU=ON L218 1- CHEM : 11 TERMS
 L221(218)SEA FILE=MEDLINE ABB=ON PLU=ON L220
 L222 1 SEA ABB=ON PLU=ON L221 AND L219

 ACT AUD006MED2B/A

L223(1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
 L224 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
 ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
 LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
 L225(9127)SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
 L226 SEL PLU=ON L223 1- CHEM : 13 TERMS
 L227(3278)SEA FILE=MEDLINE ABB=ON PLU=ON L226
 L228(2)SEA FILE=MEDLINE ABB=ON PLU=ON L227 AND L225
 L229(32)SEA FILE=MEDLINE ABB=ON PLU=ON L227 AND L224

L230 (32)SEA FILE=MEDLINE ABB=ON PLU=ON (L228 OR L229)
L231 11 SEA ABB=ON PLU=ON L230 AND PY<2003

ACT AUD006MED2A/A

L232 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L233 (1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L234 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L235 SEL PLU=ON L232 1- CHEM : 11 TERMS
L236 (218)SEA FILE=MEDLINE ABB=ON PLU=ON L235
L237 (9127)SEA FILE=MEDLINE ABB=ON PLU=ON "DRY EYE SYNDROMES"+PFT,NT/CT
L238 (1)SEA FILE=MEDLINE ABB=ON PLU=ON L236 AND L234
L239 SEL PLU=ON L233 1- CHEM : 13 TERMS
L240 (3278)SEA FILE=MEDLINE ABB=ON PLU=ON L239
L241 (2)SEA FILE=MEDLINE ABB=ON PLU=ON L240 AND L237
L242 (32)SEA FILE=MEDLINE ABB=ON PLU=ON L240 AND L234
L243 (32)SEA FILE=MEDLINE ABB=ON PLU=ON (L241 OR L242)
L244 (11)SEA FILE=MEDLINE ABB=ON PLU=ON L243 AND PY<2003
L245 20 SEA ABB=ON PLU=ON L243 NOT (L244 OR L238)

FILE 'EMBASE' ENTERED AT 07:42:25 ON 29 SEP 2005

ACT AUD006EMB1A/A

L246 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L247 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L248 SEL PLU=ON L246 1- CHEM : 11 TERMS
L249 (547)SEA FILE=EMBASE ABB=ON PLU=ON L248
L250 (2325)SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
L251 (0)SEA FILE=EMBASE ABB=ON PLU=ON L249 AND L250
L252 (1)SEA FILE=EMBASE ABB=ON PLU=ON L249 AND L247
L253 (1)SEA FILE=EMBASE ABB=ON PLU=ON (L251 OR L252)
L254 (0)SEA FILE=EMBASE ABB=ON PLU=ON L253 AND (PY<2003 OR MY<2003)
L255 1 SEA ABB=ON PLU=ON L253 NOT L254

ACT AUD006EMB2B/A

L256 (3)SEA FILE=REGISTRY ABB=ON PLU=ON 129-56-6/RN,CRN
L257 (1)SEA FILE=REGISTRY ABB=ON PLU=ON 289898-51-7/RN,CRN
L258 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L259 SEL PLU=ON L256 1- CHEM : 11 TERMS
L260 (547)SEA FILE=EMBASE ABB=ON PLU=ON L259
L261 (2325)SEA FILE=EMBASE ABB=ON PLU=ON "DRY EYE"+PFT,NT/CT
L262 (0)SEA FILE=EMBASE ABB=ON PLU=ON L260 AND L261
L263 (1)SEA FILE=EMBASE ABB=ON PLU=ON L260 AND L258
L264 (1)SEA FILE=EMBASE ABB=ON PLU=ON (L262 OR L263)
L265 (0)SEA FILE=EMBASE ABB=ON PLU=ON L264 AND (PY<2003 OR MY<2003)
L266 (1)SEA FILE=EMBASE ABB=ON PLU=ON L264 NOT L265
L267 SEL PLU=ON L257 1- CHEM : 13 TERMS
L268 (2867)SEA FILE=EMBASE ABB=ON PLU=ON L267
L269 (2)SEA FILE=EMBASE ABB=ON PLU=ON L268 AND L261

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L270 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  L268 AND L258
L271 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  (L269 OR L270)
L272 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  L271 NOT L266
L273      8 SEA ABB=ON  PLU=ON  L272 AND (PY<2003 OR MY<2003)
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      ACT AUD006EMB2A/A
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L274 (      3) SEA FILE=REGISTRY ABB=ON  PLU=ON  129-56-6/RN,CRN
L275 (      1) SEA FILE=REGISTRY ABB=ON  PLU=ON  289898-51-7/RN,CRN
L276      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
      ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
      LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L277      SEL PLU=ON  L274 1- CHEM :      11 TERMS
L278 (      547) SEA FILE=EMBASE ABB=ON  PLU=ON  L277
L279 (      2325) SEA FILE=EMBASE ABB=ON  PLU=ON  "DRY EYE"+PFT,NT/CT
L280 (      0) SEA FILE=EMBASE ABB=ON  PLU=ON  L278 AND L279
L281 (      1) SEA FILE=EMBASE ABB=ON  PLU=ON  L278 AND L276
L282 (      1) SEA FILE=EMBASE ABB=ON  PLU=ON  (L280 OR L281)
L283 (      0) SEA FILE=EMBASE ABB=ON  PLU=ON  L282 AND (PY<2003 OR MY<2003)
L284 (      1) SEA FILE=EMBASE ABB=ON  PLU=ON  L282 NOT L283
L285      SEL PLU=ON  L275 1- CHEM :      13 TERMS
L286 (      2867) SEA FILE=EMBASE ABB=ON  PLU=ON  L285
L287 (      2) SEA FILE=EMBASE ABB=ON  PLU=ON  L286 AND L279
L288 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  L286 AND L276
L289 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  (L287 OR L288)
L290 (      24) SEA FILE=EMBASE ABB=ON  PLU=ON  L289 NOT L284
L291 (      8) SEA FILE=EMBASE ABB=ON  PLU=ON  L290 AND (PY<2003 OR MY<2003)
L292      16 SEA ABB=ON  PLU=ON  L290 NOT L291
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FILE 'STNGUIDE' ENTERED AT 07:42:58 ON 29 SEP 2005
D SAVED

FILE 'BIOSIS, TOXCENTER, PASCAL, JICST-EPLUS, LIFESCI, CANCERLIT, DRUGU,
VETU, VETB, SCISEARCH' ENTERED AT 07:43:51 ON 29 SEP 2005
ACT AUD006MUL1B/A

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L293      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
L294      SEL PLU=ON  L293 1- CHEM :      11 TERMS
L295 (      813) SEA L294
L296 (      6) SEA L295 AND L293
L297 (      6) DUP REM L296 (0 DUPLICATES REMOVED)
L298      SEL PLU=ON  L293 1- CHEM :      13 TERMS
L299 (      13886) SEA L298
L300 (      139) SEA L299 AND L293
L301 (      88) DUP REM L300 (51 DUPLICATES REMOVED)
L302 (      55) SEA FILE=BIOSIS L301
L303 (      25) SEA FILE=BIOSIS L302 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L304 (      6) SEA FILE=TOXCENTER L301
L305 (      2) SEA FILE=TOXCENTER L304 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L306 (      8) SEA FILE=PASCAL L301
L307 (      2) SEA FILE=PASCAL L306 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L308 (      0) SEA FILE=JICST-EPLUS L301
L309 (      0) SEA FILE=JICST-EPLUS L308 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
L310 (      0) SEA FILE=LIFESCI L301
L311 (      0) SEA FILE=LIFESCI L310 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACR
L312 (      1) SEA FILE=CANCERLIT L301
L313 (      1) SEA FILE=CANCERLIT L312 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L314 (      11) SEA FILE=DRUGU L301

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L315(11)SEA FILE=DRUGU L314 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIM
 L316(0)SEA FILE=VETU L301
 L317(0)SEA FILE=VETU L316 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
 L318(0)SEA FILE=VETB L301
 L319(0)SEA FILE=VETB L318 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
 L320(7)SEA FILE=SCISEARCH L301
 L321(3)SEA FILE=SCISEARCH L320 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
 L322(44)SEA L301 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR LACH
 L323(3)SEA FILE=BIOSIS L297
 L324(28)SEA FILE=BIOSIS L323 OR L303
 L325(0)SEA FILE=TOXCENTER L297
 L326(2)SEA FILE=TOXCENTER L325 OR L305
 L327(0)SEA FILE=PASCAL L297
 L328(2)SEA FILE=PASCAL L327 OR L307
 L329(0)SEA FILE=JICST-EPLUS L297
 L330(0)SEA FILE=JICST-EPLUS L329 OR L309
 L331(0)SEA FILE=LIFESCI L297
 L332(0)SEA FILE=LIFESCI L331 OR L311
 L333(0)SEA FILE=CANCERLIT L297
 L334(1)SEA FILE=CANCERLIT L333 OR L313
 L335(3)SEA FILE=DRUGU L297
 L336(12)SEA FILE=DRUGU L335 OR L315
 L337(0)SEA FILE=VETU L297
 L338(0)SEA FILE=VETU L337 OR L317
 L339(0)SEA FILE=VETB L297
 L340(0)SEA FILE=VETB L339 OR L319
 L341(0)SEA FILE=SCISEARCH L297
 L342(3)SEA FILE=SCISEARCH L341 OR L321
 L343(48)SEA L297 OR L322
 L344(9)SEA FILE=BIOSIS L324 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
 L345(0)SEA FILE=TOXCENTER L326 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L346(0)SEA FILE=PASCAL L328 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
 L347(0)SEA FILE=JICST-EPLUS L330 AND (AY<2003 OR PY<2003 OR PRY<2003 O
 L348(0)SEA FILE=LIFESCI L332 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY
 L349(1)SEA FILE=CANCERLIT L334 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L350(7)SEA FILE=DRUGU L336 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2
 L351(0)SEA FILE=VETU L338 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L352(0)SEA FILE=VETB L340 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L353(1)SEA FILE=SCISEARCH L342 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L354(18)SEA L343 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
 L355(3)SEA FILE=BIOSIS L297
 L356(0)SEA FILE=BIOSIS L344 AND L355
 L357(0)SEA FILE=TOXCENTER L297
 L358(0)SEA FILE=TOXCENTER L345 AND L357
 L359(0)SEA FILE=PASCAL L297
 L360(0)SEA FILE=PASCAL L346 AND L359
 L361(0)SEA FILE=JICST-EPLUS L297
 L362(0)SEA FILE=JICST-EPLUS L347 AND L361
 L363(0)SEA FILE=LIFESCI L297
 L364(0)SEA FILE=LIFESCI L348 AND L363
 L365(0)SEA FILE=CANCERLIT L297
 L366(0)SEA FILE=CANCERLIT L349 AND L365
 L367(3)SEA FILE=DRUGU L297
 L368 1 SEA L350 AND L367
 L369(0)SEA FILE=VETU L297
 L370(0)SEA FILE=VETU L351 AND L369
 L371(0)SEA FILE=VETB L297
 L372(0)SEA FILE=VETB L352 AND L371
 L373(0)SEA FILE=SCISEARCH L297
 L374(0)SEA FILE=SCISEARCH L353 AND L373

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L375      1 SEA ABB=ON  PLU=ON  L354 AND L297
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          ACT AUD006MUL1A/A
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L376      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
L377      SEL PLU=ON  L376 1-  CHEM :          11 TERMS
L378(
L379(      813)SEA L377
L380(      6)SEA L378 AND L376
L381(      6)DUP REM L379 (0 DUPLICATES REMOVED)
L382(      SEL PLU=ON  L376 1-  CHEM :          13 TERMS
13886)SEA L381
L383(      139)SEA L382 AND L376
L384(      88)DUP REM L383 (51 DUPLICATES REMOVED)
L385(      55)SEA FILE=BIOSIS L384
L386(      25)SEA FILE=BIOSIS L385 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L387(      6)SEA FILE=TOXCENTER L384
L388(      2)SEA FILE=TOXCENTER L387 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L389(      8)SEA FILE=PASCAL L384
L390(      2)SEA FILE=PASCAL L389 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L391(      0)SEA FILE=JICST-EPLUS L384
L392(      0)SEA FILE=JICST-EPLUS L391 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
L393(      0)SEA FILE=LIFESCI L384
L394(      0)SEA FILE=LIFESCI L393 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACR
L395(      1)SEA FILE=CANCERLIT L384
L396(      1)SEA FILE=CANCERLIT L395 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L397(      11)SEA FILE=DRUGU L384
L398(      11)SEA FILE=DRUGU L397 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIM
L399(      0)SEA FILE=VETU L384
L400(      0)SEA FILE=VETU L399 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
L401(      0)SEA FILE=VETB L384
L402(      0)SEA FILE=VETB L401 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
L403(      7)SEA FILE=SCISEARCH L384
L404(      3)SEA FILE=SCISEARCH L403 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L405(      44)SEA L384 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA? OR LACH
L406(      3)SEA FILE=BIOSIS L380
L407(      28)SEA FILE=BIOSIS L406 OR L386
L408(      0)SEA FILE=TOXCENTER L380
L409(      2)SEA FILE=TOXCENTER L408 OR L388
L410(      0)SEA FILE=PASCAL L380
L411(      2)SEA FILE=PASCAL L410 OR L390
L412(      0)SEA FILE=JICST-EPLUS L380
L413(      0)SEA FILE=JICST-EPLUS L412 OR L392
L414(      0)SEA FILE=LIFESCI L380
L415(      0)SEA FILE=LIFESCI L414 OR L394
L416(      0)SEA FILE=CANCERLIT L380
L417(      1)SEA FILE=CANCERLIT L416 OR L396
L418(      3)SEA FILE=DRUGU L380
L419(      12)SEA FILE=DRUGU L418 OR L398
L420(      0)SEA FILE=VETU L380
L421(      0)SEA FILE=VETU L420 OR L400
L422(      0)SEA FILE=VETB L380
L423(      0)SEA FILE=VETB L422 OR L402
L424(      0)SEA FILE=SCISEARCH L380
L425(      3)SEA FILE=SCISEARCH L424 OR L404
L426(      48)SEA L380 OR L405
L427(      9)SEA FILE=BIOSIS L407 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
L428(      0)SEA FILE=TOXCENTER L409 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
L429(      0)SEA FILE=PASCAL L411 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
L430(      0)SEA FILE=JICST-EPLUS L413 AND (AY<2003 OR PY<2003 OR PRY<2003 O
L431(      0)SEA FILE=LIFESCI L415 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY

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L432(1)SEA FILE=CANCERLIT L417 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L433(7)SEA FILE=DRUGU L419 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2
 L434(0)SEA FILE=VETU L421 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L435(0)SEA FILE=VETB L423 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L436(1)SEA FILE=SCISEARCH L425 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L437(18)SEA L426 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
 L438(3)SEA FILE=BIOSIS L380
 L439(0)SEA FILE=BIOSIS L427 AND L438
 L440(0)SEA FILE=TOXCENTER L380
 L441(0)SEA FILE=TOXCENTER L428 AND L440
 L442(0)SEA FILE=PASCAL L380
 L443(0)SEA FILE=PASCAL L429 AND L442
 L444(0)SEA FILE=JICST-EPLUS L380
 L445(0)SEA FILE=JICST-EPLUS L430 AND L444
 L446(0)SEA FILE=LIFESCI L380
 L447(0)SEA FILE=LIFESCI L431 AND L446
 L448(0)SEA FILE=CANCERLIT L380
 L449(0)SEA FILE=CANCERLIT L432 AND L448
 L450(3)SEA FILE=DRUGU L380
 L451(1)SEA FILE=DRUGU L433 AND L450
 L452(0)SEA FILE=VETU L380
 L453(0)SEA FILE=VETU L434 AND L452
 L454(0)SEA FILE=VETB L380
 L455(0)SEA FILE=VETB L435 AND L454
 L456(0)SEA FILE=SCISEARCH L380
 L457(0)SEA FILE=SCISEARCH L436 AND L456
 L458(1)SEA L437 AND L380
 L459(3)SEA FILE=BIOSIS L380
 L460 3 SEA L459 NOT L439
 L461(0)SEA FILE=TOXCENTER L380
 L462(0)SEA FILE=TOXCENTER L461 NOT L441
 L463(0)SEA FILE=PASCAL L380
 L464(0)SEA FILE=PASCAL L463 NOT L443
 L465(0)SEA FILE=JICST-EPLUS L380
 L466(0)SEA FILE=JICST-EPLUS L465 NOT L445
 L467(0)SEA FILE=LIFESCI L380
 L468(0)SEA FILE=LIFESCI L467 NOT L447
 L469(0)SEA FILE=CANCERLIT L380
 L470(0)SEA FILE=CANCERLIT L469 NOT L449
 L471(3)SEA FILE=DRUGU L380
 L472 2 SEA L471 NOT L451
 L473(0)SEA FILE=VETU L380
 L474(0)SEA FILE=VETU L473 NOT L453
 L475(0)SEA FILE=VETB L380
 L476(0)SEA FILE=VETB L475 NOT L455
 L477(0)SEA FILE=SCISEARCH L380
 L478(0)SEA FILE=SCISEARCH L477 NOT L457
 L479 5 SEA ABB=ON PLU=ON L380 NOT L458

 ACT AUD006MUL2B/A

L480 QUE ABB=ON PLU=ON EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
 L481 SEL PLU=ON L480 1- CHEM : 11 TERMS
 L482(813)SEA L481
 L483(6)SEA L482 AND L480
 L484(6)DUP REM L483 (0 DUPLICATES REMOVED)
 L485 SEL PLU=ON L480 1- CHEM : 13 TERMS
 L486(13886)SEA L485
 L487(139)SEA L486 AND L480
 L488(88)DUP REM L487 (51 DUPLICATES REMOVED)

L489(55)SEA FILE=BIOSIS L488
 L490(25)SEA FILE=BIOSIS L489 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
 L491(6)SEA FILE=TOXCENTER L488
 L492(2)SEA FILE=TOXCENTER L491 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
 L493(8)SEA FILE=PASCAL L488
 L494(2)SEA FILE=PASCAL L493 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
 L495(0)SEA FILE=JICST-EPLUS L488
 L496(0)SEA FILE=JICST-EPLUS L495 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
 L497(0)SEA FILE=LIFESCI L488
 L498(0)SEA FILE=LIFESCI L497 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACR
 L499(1)SEA FILE=CANCERLIT L488
 L500(1)SEA FILE=CANCERLIT L499 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
 L501(11)SEA FILE=DRUGU L488
 L502(11)SEA FILE=DRUGU L501 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIM
 L503(0)SEA FILE=VETU L488
 L504(0)SEA FILE=VETU L503 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
 L505(0)SEA FILE=VETB L488
 L506(0)SEA FILE=VETB L505 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
 L507(7)SEA FILE=SCISEARCH L488
 L508(3)SEA FILE=SCISEARCH L507 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
 L509(44)SEA L488 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR LACH
 L510(3)SEA FILE=BIOSIS L484
 L511(28)SEA FILE=BIOSIS L510 OR L490
 L512(0)SEA FILE=TOXCENTER L484
 L513(2)SEA FILE=TOXCENTER L512 OR L492
 L514(0)SEA FILE=PASCAL L484
 L515(2)SEA FILE=PASCAL L514 OR L494
 L516(0)SEA FILE=JICST-EPLUS L484
 L517(0)SEA FILE=JICST-EPLUS L516 OR L496
 L518(0)SEA FILE=LIFESCI L484
 L519(0)SEA FILE=LIFESCI L518 OR L498
 L520(0)SEA FILE=CANCERLIT L484
 L521(1)SEA FILE=CANCERLIT L520 OR L500
 L522(3)SEA FILE=DRUGU L484
 L523(12)SEA FILE=DRUGU L522 OR L502
 L524(0)SEA FILE=VETU L484
 L525(0)SEA FILE=VETU L524 OR L504
 L526(0)SEA FILE=VETB L484
 L527(0)SEA FILE=VETB L526 OR L506
 L528(0)SEA FILE=SCISEARCH L484
 L529(3)SEA FILE=SCISEARCH L528 OR L508
 L530(48)SEA L484 OR L509
 L531(9)SEA FILE=BIOSIS L511 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
 L532(0)SEA FILE=TOXCENTER L513 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L533(0)SEA FILE=PASCAL L515 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
 L534(0)SEA FILE=JICST-EPLUS L517 AND (AY<2003 OR PY<2003 OR PRY<2003 O
 L535(0)SEA FILE=LIFESCI L519 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY
 L536(1)SEA FILE=CANCERLIT L521 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L537(7)SEA FILE=DRUGU L523 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2
 L538(0)SEA FILE=VETU L525 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L539(0)SEA FILE=VETB L527 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
 L540(1)SEA FILE=SCISEARCH L529 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
 L541(18)SEA L530 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
 L542 9 SEA L531 AND L490
 L543(0)SEA FILE=TOXCENTER L532 AND L492
 L544(0)SEA FILE=PASCAL L533 AND L494
 L545(0)SEA FILE=JICST-EPLUS L534 AND L496
 L546(0)SEA FILE=LIFESCI L535 AND L498
 L547 1 SEA L536 AND L500
 L548 6 SEA L537 AND L502

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L549(      0)SEA FILE=VETU L538 AND L504
L550(      0)SEA FILE=VETB L539 AND L506
L551      1 SEA L540 AND L508
L552     17 SEA ABB=ON  PLU=ON  L541 AND L509
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          ACT AUD006MUL2A/A
-----
L553      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
L554      SEL PLU=ON  L553 1-  CHEM :          11 TERMS
L555(    813)SEA L554
L556(      6)SEA L555 AND L553
L557(      6)DUP REM L556 (0 DUPLICATES REMOVED)
L558      SEL PLU=ON  L553 1-  CHEM :          13 TERMS
L559(   13886)SEA L558
L560(    139)SEA L559 AND L553
L561(     88)DUP REM L560 (51 DUPLICATES REMOVED)
L562(     55)SEA FILE=BIOSIS L561
L563(    25)SEA FILE=BIOSIS L562 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L564(      6)SEA FILE=TOXCENTER L561
L565(      2)SEA FILE=TOXCENTER L564 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L566(      8)SEA FILE=PASCAL L561
L567(      2)SEA FILE=PASCAL L566 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRI
L568(      0)SEA FILE=JICST-EPLUS L561
L569(      0)SEA FILE=JICST-EPLUS L568 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR
L570(      0)SEA FILE=LIFESCI L561
L571(      0)SEA FILE=LIFESCI L570 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACR
L572(      1)SEA FILE=CANCERLIT L561
L573(      1)SEA FILE=CANCERLIT L572 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L574(    11)SEA FILE=DRUGU L561
L575(    11)SEA FILE=DRUGU L574 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIM
L576(      0)SEA FILE=VETU L561
L577(      0)SEA FILE=VETU L576 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
L578(      0)SEA FILE=VETB L561
L579(      0)SEA FILE=VETB L578 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LACRIMA
L580(      7)SEA FILE=SCISEARCH L561
L581(      3)SEA FILE=SCISEARCH L580 AND ((DRY?(3A)EYE?) OR ?REFRACTI? OR LA
L582(    44)SEA L561 AND ((DRY?(3A) EYE?) OR ?REFRACTI? OR LACRIMA? OR LACH
L583(      3)SEA FILE=BIOSIS L557
L584(    28)SEA FILE=BIOSIS L583 OR L563
L585(      0)SEA FILE=TOXCENTER L557
L586(      2)SEA FILE=TOXCENTER L585 OR L565
L587(      0)SEA FILE=PASCAL L557
L588(      2)SEA FILE=PASCAL L587 OR L567
L589(      0)SEA FILE=JICST-EPLUS L557
L590(      0)SEA FILE=JICST-EPLUS L589 OR L569
L591(      0)SEA FILE=LIFESCI L557
L592(      0)SEA FILE=LIFESCI L591 OR L571
L593(      0)SEA FILE=CANCERLIT L557
L594(      1)SEA FILE=CANCERLIT L593 OR L573
L595(      3)SEA FILE=DRUGU L557
L596(    12)SEA FILE=DRUGU L595 OR L575
L597(      0)SEA FILE=VETU L557
L598(      0)SEA FILE=VETU L597 OR L577
L599(      0)SEA FILE=VETB L557
L600(      0)SEA FILE=VETB L599 OR L579
L601(      0)SEA FILE=SCISEARCH L557
L602(      3)SEA FILE=SCISEARCH L601 OR L581
L603(    48)SEA L557 OR L582
L604(      9)SEA FILE=BIOSIS L584 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
L605(      0)SEA FILE=TOXCENTER L586 AND (AY<2003 OR PY<2003 OR PRY<2003 OR

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L606(0)SEA FILE=PASCAL L588 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<
L607(0)SEA FILE=JICST-EPLUS L590 AND (AY<2003 OR PY<2003 OR PRY<2003 O
L608(0)SEA FILE=LIFESCI L592 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY
L609(1)SEA FILE=CANCERLIT L594 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
L610(7)SEA FILE=DRUGU L596 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2
L611(0)SEA FILE=VETU L598 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
L612(0)SEA FILE=VETB L600 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<20
L613(1)SEA FILE=SCISEARCH L602 AND (AY<2003 OR PY<2003 OR PRY<2003 OR
L614(18)SEA L603 AND (AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003)
L615(9)SEA FILE=BIOSIS L604 AND L563
L616(0)SEA FILE=TOXCENTER L605 AND L565
L617(0)SEA FILE=PASCAL L606 AND L567
L618(0)SEA FILE=JICST-EPLUS L607 AND L569
L619(0)SEA FILE=LIFESCI L608 AND L571
L620(1)SEA FILE=CANCERLIT L609 AND L573
L621(6)SEA FILE=DRUGU L610 AND L575
L622(0)SEA FILE=VETU L611 AND L577
L623(0)SEA FILE=VETB L612 AND L579
L624(1)SEA FILE=SCISEARCH L613 AND L581
L625(17)SEA L614 AND L582
L626 16 SEA L563 NOT L615
L627 2 SEA L565 NOT L616
L628 2 SEA L567 NOT L617
L629(0)SEA FILE=JICST-EPLUS L569 NOT L618
L630(0)SEA FILE=LIFESCI L571 NOT L619
L631(0)SEA FILE=CANCERLIT L573 NOT L620
L632 5 SEA L575 NOT L621
L633(0)SEA FILE=VETU L577 NOT L622
L634(0)SEA FILE=VETB L579 NOT L623
L635 2 SEA L581 NOT L624
L636 27 SEA ABB=ON PLU=ON L582 NOT L625

FILE 'STNGUIDE' ENTERED AT 07:44:57 ON 29 SEP 2005
D SAVED

FILE 'HCAPLUS' ENTERED AT 07:45:15 ON 29 SEP 2005

FILE 'STNGUIDE' ENTERED AT 07:45:33 ON 29 SEP 2005

FILE 'REGISTRY' ENTERED AT 07:46:37 ON 29 SEP 2005

FILE 'ZCAPLUS' ENTERED AT 07:46:40 ON 29 SEP 2005

FILE 'HCAPLUS' ENTERED AT 07:46:43 ON 29 SEP 2005

FILE 'USPATFULL' ENTERED AT 07:46:48 ON 29 SEP 2005

FILE 'USPATFULL, USPAT2' ENTERED AT 07:46:52 ON 29 SEP 2005

FILE 'USPAT2' ENTERED AT 07:47:03 ON 29 SEP 2005

FILE 'WPIX' ENTERED AT 07:47:09 ON 29 SEP 2005

FILE 'MEDLINE' ENTERED AT 07:47:17 ON 29 SEP 2005

FILE 'EMBASE' ENTERED AT 07:47:21 ON 29 SEP 2005

FILE 'BIOSIS' ENTERED AT 07:47:24 ON 29 SEP 2005

FILE 'TOXCENTER' ENTERED AT 07:47:43 ON 29 SEP 2005

FILE 'PASCAL' ENTERED AT 07:47:46 ON 29 SEP 2005

FILE 'JICST-EPLUS' ENTERED AT 07:47:50 ON 29 SEP 2005

FILE 'LIFESCI' ENTERED AT 07:47:54 ON 29 SEP 2005

FILE 'CANCERLIT' ENTERED AT 07:48:00 ON 29 SEP 2005

FILE 'DRUGU' ENTERED AT 07:48:03 ON 29 SEP 2005

FILE 'VETU' ENTERED AT 07:48:08 ON 29 SEP 2005

FILE 'VETB' ENTERED AT 07:48:12 ON 29 SEP 2005

FILE 'SCISEARCH' ENTERED AT 07:48:17 ON 29 SEP 2005

FILE 'HCAPLUS' ENTERED AT 07:48:19 ON 29 SEP 2005

FILE 'STNGUIDE' ENTERED AT 07:48:22 ON 29 SEP 2005

D QUE L55

D QUE L170

D QUE L375

L637 FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:49:00 ON 29 SEP 2005
13 DUP REM L55 L132 L170 L375 (4 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE HCAPLUS
ANSWERS '4-9' FROM FILE USPATFULL
ANSWERS '10-12' FROM FILE WPIX
ANSWER '13' FROM FILE DRUGU

FILE 'STNGUIDE' ENTERED AT 07:49:08 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:49:32 ON 29 SEP 2005
D IBIB ED AB HITIND HITSTR RETABLE

FILE 'STNGUIDE' ENTERED AT 07:49:34 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:50:00 ON 29 SEP 2005
D IBIB ED AB HITIND HITSTR RETABLE 2-3

FILE 'STNGUIDE' ENTERED AT 07:50:02 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:50:33 ON 29 SEP 2005
D IBIB AB HITSTR 4-9

FILE 'STNGUIDE' ENTERED AT 07:50:36 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:51:25 ON 29 SEP 2005
D IALL ABEQ TECH ABEX 10-12

FILE 'STNGUIDE' ENTERED AT 07:51:28 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, DRUGU' ENTERED AT 07:51:55 ON 29 SEP 2005
D IBIB ED AB HITIND 13

FILE 'STNGUIDE' ENTERED AT 07:52:06 ON 29 SEP 2005
D QUE L101
D QUE L143

D QUE L201
D QUE L231
D QUE L273
D QUE L552

FILE 'HCAPLUS, USPATFULL, USPAT2, WPIX, MEDLINE, EMBASE, BIOSIS,
CANCERLIT, DRUGU, SCISEARCH' ENTERED AT 07:53:36 ON 29 SEP 2005

L638 94 DUP REM L101 L143 L201 L231 L273 L552 (21 DUPLICATES REMOVED)
ANSWERS '1-31' FROM FILE HCAPLUS
ANSWERS '32-52' FROM FILE USPATFULL
ANSWERS '53-76' FROM FILE WPIX
ANSWERS '77-81' FROM FILE MEDLINE
ANSWERS '82-87' FROM FILE BIOSIS
ANSWERS '88-93' FROM FILE DRUGU
ANSWER '94' FROM FILE SCISEARCH

FILE 'STNGUIDE' ENTERED AT 07:53:46 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH'
ENTERED AT 07:54:17 ON 29 SEP 2005

D IBIB ED AB HITIND HITSTR

FILE 'STNGUIDE' ENTERED AT 07:54:18 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH'
ENTERED AT 07:54:32 ON 29 SEP 2005

D IBIB ED AB HITIND HITSTR 2-31

FILE 'STNGUIDE' ENTERED AT 07:54:41 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH'
ENTERED AT 07:55:40 ON 29 SEP 2005

D IBIB AB HITSTR 32-52

FILE 'STNGUIDE' ENTERED AT 07:55:48 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH'
ENTERED AT 07:56:07 ON 29 SEP 2005

D IALL ABEQ TECH ABEX 53-76

FILE 'STNGUIDE' ENTERED AT 07:56:38 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, BIOSIS, DRUGU, SCISEARCH'
ENTERED AT 07:57:19 ON 29 SEP 2005

D IBIB ED AB HITIND 77-

FILE 'STNGUIDE' ENTERED AT 07:57:25 ON 29 SEP 2005

D QUE L78
D QUE L186
D QUE L222
D QUE L255
D QUE L479

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, DRUGU' ENTERED AT 07:58:28
ON 29 SEP 2005

L639 12 DUP REM L78 L186 L222 L255 L479 (0 DUPLICATES REMOVED)
ANSWERS '1-2' FROM FILE HCAPLUS
ANSWERS '3-5' FROM FILE WPIX
ANSWER '6' FROM FILE MEDLINE
ANSWER '7' FROM FILE EMBASE

ANSWERS '8-10' FROM FILE BIOSIS
ANSWERS '11-12' FROM FILE DRUGU

FILE 'STNGUIDE' ENTERED AT 07:58:45 ON 29 SEP 2005

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, DRUGU' ENTERED AT 07:58:59
ON 29 SEP 2005

D IBIB ED AB HITIND HITSTR RETABLE 1-2

FILE 'STNGUIDE' ENTERED AT 07:59:00 ON 29 SEP 2005

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, DRUGU' ENTERED AT 07:59:17
ON 29 SEP 2005

D IALL ABEQ TECH ABEX 3-5

FILE 'STNGUIDE' ENTERED AT 07:59:20 ON 29 SEP 2005

FILE 'HCAPLUS, WPIX, MEDLINE, EMBASE, BIOSIS, DRUGU' ENTERED AT 08:00:01
ON 29 SEP 2005

D IBIB ED AB HITIND 6-

FILE 'STNGUIDE' ENTERED AT 08:00:04 ON 29 SEP 2005

D QUE L125

D QUE L155

D QUE L217

D QUE L245

D QUE L292

D QUE L636

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER,
PASCAL, DRUGU, SCISEARCH' ENTERED AT 08:01:10 ON 29 SEP 2005

L640 79 DUP REM L125 L155 L217 L245 L292 L636 (32 DUPLICATES REMOVED)

ANSWERS '1-32' FROM FILE HCAPLUS

ANSWERS '33-37' FROM FILE USPATFULL

ANSWERS '38-48' FROM FILE WPIX

ANSWERS '49-60' FROM FILE MEDLINE

ANSWERS '61-63' FROM FILE EMBASE

ANSWERS '64-71' FROM FILE BIOSIS

ANSWER '72' FROM FILE TOXCENTER

ANSWERS '73-77' FROM FILE DRUGU

ANSWERS '78-79' FROM FILE SCISEARCH

FILE 'STNGUIDE' ENTERED AT 08:01:40 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER,
DRUGU, SCISEARCH' ENTERED AT 08:01:54 ON 29 SEP 2005

D IBIB ED AB HITIND HITSTR 1-32

FILE 'STNGUIDE' ENTERED AT 08:02:13 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER,
DRUGU, SCISEARCH' ENTERED AT 08:02:43 ON 29 SEP 2005

D IBIB AB HITSTR 33-37

FILE 'STNGUIDE' ENTERED AT 08:02:45 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER,
DRUGU, SCISEARCH' ENTERED AT 08:03:03 ON 29 SEP 2005

D IALL ABEQ TECH ABEX 38-48

FILE 'STNGUIDE' ENTERED AT 08:03:11 ON 29 SEP 2005

FILE 'HCAPLUS, USPATFULL, WPIX, MEDLINE, EMBASE, BIOSIS, TOXCENTER,
DRUGU, SCISEARCH' ENTERED AT 08:03:40 ON 29 SEP 2005
D IBIB ED AB HITIND 49-

FILE 'STNGUIDE' ENTERED AT 08:03:49 ON 29 SEP 2005

FILE 'STNGUIDE' ENTERED AT 08:04:24 ON 29 SEP 2005

FILE HOME

FILE HCAPLUS

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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)

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FILE USPATFULL

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US6951031
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210555
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
>>> published document but also a list of any subsequent <<<
>>> publications. The publication number, patent kind code, and <<<
>>> publication date for all the US publications for an invention <<<
>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
>>> records and may be searched in standard search fields, e.g., /PN, <<<
>>> /PK, etc. <<<

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>>> classifications, or claims, that may potentially change from <<<
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FILE USPAT2

FILE COVERS 2001 TO PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US2005202247
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210551
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

USPAT2 is a companion file to USPATFULL. USPAT2 contains full text of the latest US publications, starting in 2001, for the inventions covered in USPATFULL. USPATFULL contains full text of the original published US patents from 1971 to date and the original applications from 2001. In addition, a USPATFULL record for an invention contains a complete list of publications that may be searched in standard search fields, e.g., /PN, /PK, etc.

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FILE WPIX

FILE LAST UPDATED: 28 SEP 2005 <20050928/UP>
MOST RECENT DERWENT UPDATE: 200562 <200562/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
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PLEASE CHECK:
<http://thomsonderwent.com/support/dwpioref/reftools/classification/code-rev>
FOR DETAILS. <<<

FILE MEDLINE

FILE LAST UPDATED: 28 SEP 2005 (20050928/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow prompt (=>). See also:

<http://www.nlm.nih.gov/mesh/>
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

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FILE EMBASE

FILE COVERS 1974 TO 22 Sep 2005 (20050922/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE STNGUIDE

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Sep 23, 2005 (20050923/UP).

FILE BIOSIS

FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 28 September 2005 (20050928/ED)

FILE RELOADED: 19 October 2003.

FILE TOXCENTER

FILE COVERS 1907 TO 27 Sep 2005 (20050927/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TOXCENTER has been enhanced with new files segments and search fields. See HELP CONTENT for more information.

TOXCENTER thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary. See <http://www.nlm.nih.gov/mesh/> and http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html for a description of changes.

FILE PASCAL

FILE LAST UPDATED: 26 SEP 2005 <20050926/UP>

FILE COVERS 1977 TO DATE.

>>> SIMULTANEOUS LEFT AND RIGHT TRUNCATION IS AVAILABLE

IN THE BASIC INDEX (/BI) FIELD <<<

FILE JICST-EPLUS

FILE COVERS 1985 TO 26 SEP 2005 (20050926/ED)

THE JICST-EPLUS FILE HAS BEEN RELOADED TO REFLECT THE 1999 CONTROLLED TERM (/CT) THESAURUS RELOAD.

FILE LIFESCI

FILE COVERS 1978 TO 19 Sep 2005 (20050919/ED)

FILE CANCERLIT

FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MESH 2002 vocabulary. Enter HELP THESAURUS for details.

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FILE DRUGU

FILE LAST UPDATED: 27 SEP 2005 <20050927/UP>

>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<

>>> THESAURUS AVAILABLE IN /CT <<<

FILE VETU

FILE LAST UPDATED: 02 JAN 2002 <20020102/UP>

FILE COVERS 1983-2001

FILE VETB

FILE LAST UPDATED: 25 SEP 94 <940925/UP>

FILE COVERS 1968-1982

FILE SCISEARCH

FILE COVERS 1974 TO 22 Sep 2005 (20050922/ED)

SCISEARCH has been reloaded, see HELP RLOAD for details.

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 SEP 2005 HIGHEST RN 864132-17-2

DICTIONARY FILE UPDATES: 28 SEP 2005 HIGHEST RN 864132-17-2

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

*

*

* The CA roles and document type information have been removed from *
 * the IDE default display format and the ED field has been added, *
 * effective March 20, 2005. A new display format, IDERL, is now *
 * available and contains the CA role and document type information. *
 *

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

FILE ZCAPLUS

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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14
 FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)

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=> => d his ful

(FILE 'STNGUIDE' ENTERED AT 08:04:24 ON 29 SEP 2005)
 DEL HIS

FILE 'HCAPLUS' ENTERED AT 08:58:38 ON 29 SEP 2005
 ACT AUD006MULINV/A

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L1 (      3)SEA ABB=ON  PLU=ON  129-56-6/RN,CRN
L2      QUE ABB=ON  PLU=ON  EYE OR EYES OR OCULA? OR ?OPHTHALM? OR
      ?OPHTHALM? OR ?KERATO? OR ?KERATITIS? OR ?KERATECT? OR
      ?REFRACTI? OR ?CORNEA? OR TEAR OR TEARS OR LACRIMA? OR
      LACHRYMA? OR ?CONJUNCTIV? OR ?SJOGREN? OR ?XEROPHTHAL?
L3      QUE ABB=ON  PLU=ON  JNK OR JNK1 OR P46JNK OR ((MITOGEN OR JUN)
      (5A) ?KINAS?)
L4 (      67)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L5 (      41)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L6 (      26)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L7 (      31)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L8 (      55)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L9 (      19)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L10 (      0)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L11 (      9)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L12 (      6)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L13 (     14)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU

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L14 (      0)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L15 (      0)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L16 (     48)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L17 (      0)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L18 (      5)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L19 (      2)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L20 (    323)SEA ABB=ON  PLU=ON  GAMACHE, D?/AU
L21 (      SEL ABB=ON  PLU=ON  L1 1- CHEM :      11 TERMS
L22 (    432)SEA ABB=ON  PLU=ON  L21
L23 (     22)SEA ABB=ON  PLU=ON  L21
L24 (    218)SEA ABB=ON  PLU=ON  L21
L25 (    547)SEA ABB=ON  PLU=ON  L21
L26 (    337)SEA ABB=ON  PLU=ON  L21
L27 (     22)SEA ABB=ON  PLU=ON  L21
L28 (      1)SEA ABB=ON  PLU=ON  L21
L29 (     10)SEA ABB=ON  PLU=ON  L21
L30 (     10)SEA ABB=ON  PLU=ON  L21
L31 (    201)SEA ABB=ON  PLU=ON  L21
L32 (      0)SEA ABB=ON  PLU=ON  L21
L33 (      0)SEA ABB=ON  PLU=ON  L21
L34 (     72)SEA ABB=ON  PLU=ON  L21
L35 (      0)SEA ABB=ON  PLU=ON  L21
L36 (      2)SEA ABB=ON  PLU=ON  L21
L37 (      0)SEA ABB=ON  PLU=ON  L21
L38 (   1874)SEA ABB=ON  PLU=ON  L21
L39 (     46)SEA ABB=ON  PLU=ON  L4 AND (L22 OR L3 OR L2)
L40 (     30)SEA ABB=ON  PLU=ON  L5 AND (L23 OR L3 OR L2)
L41 (     17)SEA ABB=ON  PLU=ON  L6 AND (L24 OR L3 OR L2)
L42 (     16)SEA ABB=ON  PLU=ON  L7 AND (L25 OR L3 OR L2)
L43 (     31)SEA ABB=ON  PLU=ON  L8 AND (L26 OR L3 OR L2)
L44 (      8)SEA ABB=ON  PLU=ON  L9 AND (L27 OR L3 OR L2)
L45 (      0)SEA ABB=ON  PLU=ON  L10 AND (L28 OR L3 OR L2)
L46 (      6)SEA ABB=ON  PLU=ON  L11 AND (L29 OR L3 OR L2)
L47 (      5)SEA ABB=ON  PLU=ON  L12 AND (L30 OR L3 OR L2)
L48 (     11)SEA ABB=ON  PLU=ON  L13 AND (L31 OR L3 OR L2)
L49 (      0)SEA ABB=ON  PLU=ON  L14 AND (L32 OR L3 OR L2)
L50 (      0)SEA ABB=ON  PLU=ON  L15 AND (L33 OR L3 OR L2)
L51 (     23)SEA ABB=ON  PLU=ON  L16 AND (L34 OR L3 OR L2)
L52 (      0)SEA ABB=ON  PLU=ON  L17 AND (L35 OR L3 OR L2)
L53 (      0)SEA ABB=ON  PLU=ON  L18 AND (L36 OR L3 OR L2)
L54 (      0)SEA ABB=ON  PLU=ON  L19 AND (L37 OR L3 OR L2)
L55 (    193)SEA ABB=ON  PLU=ON  L20 AND (L38 OR L3 OR L2)
L56 (     72)DUP REM L55 (121 DUPLICATES REMOVED)
L57 (     45)SEA L56
L58 (     45)SEA L57 AND (L22 OR L39)
L59 (      2)SEA L56
L60 (      2)SEA L59 AND (L23 OR L40)
L61 (      2)SEA L56
L62 (      2)SEA L61 AND (L24 OR L41)
L63 (      0)SEA L56
L64 (      0)SEA L63 AND (L25 OR L42)
L65 (     18)SEA L56
L66 (     18)SEA L65 AND (L26 OR L43)
L67 (      0)SEA L56
L68 (      0)SEA L67 AND (L27 OR L44)
L69 (      0)SEA L56
L70 (      0)SEA L69 AND (L28 OR L45)
L71 (      0)SEA L56
L72 (      0)SEA L71 AND (L29 OR L46)
L73 (      0)SEA L56

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L74 (      0)SEA L73 AND (L30 OR L47)
L75 (      2)SEA L56
L76 (      2)SEA L75 AND (L31 OR L48)
L77 (      0)SEA L56
L78 (      0)SEA L77 AND (L32 OR L49)
L79 (      0)SEA L56
L80 (      0)SEA L79 AND (L33 OR L50)
L81 (      3)SEA L56
L82 (      3)SEA L81 AND (L34 OR L51)
L83 (      0)SEA L56
L84 (      0)SEA L83 AND (L35 OR L52)
L85 (      0)SEA L56
L86 (      0)SEA L85 AND (L36 OR L53)
L87 (      0)SEA L56
L88 (      0)SEA L87 AND (L37 OR L54)
L89 (      72)SEA ABB=ON PLU=ON L56 AND (L38 OR L55)
L90 (      45)SEA L56
L91 (      1)SEA L90 AND (L22 OR L3)
L92 (      2)SEA L56
L93 (      0)SEA L92 AND (L23 OR L3)
L94 (      2)SEA L56
L95 (      0)SEA L94 AND (L24 OR L3)
L96 (      0)SEA L56
L97 (      0)SEA L96 AND (L25 OR L3)
L98 (      18)SEA L56
L99 (      0)SEA L98 AND (L26 OR L3)
L100 (      0)SEA FILE=PASCAL L56
L101 (      0)SEA FILE=PASCAL L100 AND (L27 OR L3)
L102 (      0)SEA FILE=JICST-EPLUS L56
L103 (      0)SEA FILE=JICST-EPLUS L102 AND (L28 OR L3)
L104 (      0)SEA FILE=LIFESCI L56
L105 (      0)SEA FILE=LIFESCI L104 AND (L29 OR L3)
L106 (      0)SEA FILE=CANCERLIT L56
L107 (      0)SEA FILE=CANCERLIT L106 AND (L30 OR L3)
L108 (      2)SEA FILE=DRUGU L56
L109 (      0)SEA FILE=DRUGU L108 AND (L31 OR L3)
L110 (      0)SEA FILE=VETU L56
L111 (      0)SEA FILE=VETU L110 AND (L32 OR L3)
L112 (      0)SEA FILE=VETB L56
L113 (      0)SEA FILE=VETB L112 AND (L33 OR L3)
L114 (      3)SEA FILE=SCISEARCH L56
L115 (      0)SEA FILE=SCISEARCH L114 AND (L34 OR L3)
L116 (      0)SEA FILE=CONF L56
L117 (      0)SEA FILE=CONF L116 AND (L35 OR L3)
L118 (      0)SEA FILE=CONFSCI L56
L119 (      0)SEA FILE=CONFSCI L118 AND (L36 OR L3)
L120 (      0)SEA FILE=DISSABS L56
L121 (      0)SEA FILE=DISSABS L120 AND (L37 OR L3)
L122 (      1)SEA L56 AND (L38 OR L3)
L123 (      42)SEA FILE=HCAPLUS L58 AND ALCON/PA,CS,SO
L124 (      2)SEA FILE=WPIX L60 AND ALCON/PA,CS,SO
L125 (      2)SEA FILE=MEDLINE L62 AND ALCON/PA,CS,SO
L126 (      0)SEA FILE=EMBASE L64 AND ALCON/PA,CS,SO
L127 (      16)SEA FILE=BIOSIS L66 AND ALCON/PA,CS,SO
L128 (      0)SEA FILE=PASCAL L68 AND ALCON/PA,CS,SO
L129 (      0)SEA FILE=JICST-EPLUS L70 AND ALCON/PA,CS,SO
L130 (      0)SEA FILE=LIFESCI L72 AND ALCON/PA,CS,SO
L131 (      0)SEA FILE=CANCERLIT L74 AND ALCON/PA,CS,SO
L132 (      2)SEA FILE=DRUGU L76 AND ALCON/PA,CS,SO
L133 (      0)SEA FILE=VETU L78 AND ALCON/PA,CS,SO

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L134 (0)SEA FILE=VETB L80 AND ALCON/PA,CS,SO
 L135 (2)SEA FILE=SCISEARCH L82 AND ALCON/PA,CS,SO
 L136 (0)SEA FILE=CONF L84 AND ALCON/PA,CS,SO
 L137 (0)SEA FILE=CONFSCI L86 AND ALCON/PA,CS,SO
 L138 (0)SEA FILE=DISSABS L88 AND ALCON/PA,CS,SO
 L139 (66)SEA L89 AND ALCON/PA,CS,SO
 L140 (42)SEA FILE=HCAPLUS L123 AND L2
 L141 (2)SEA FILE=WPIX L124 AND L2
 L142 (2)SEA FILE=MEDLINE L125 AND L2
 L143 (0)SEA FILE=EMBASE L126 AND L2
 L144 (16)SEA FILE=BIOSIS L127 AND L2
 L145 (0)SEA FILE=PASCAL L128 AND L2
 L146 (0)SEA FILE=JICST-EPLUS L129 AND L2
 L147 (0)SEA FILE=LIFESCI L130 AND L2
 L148 (0)SEA FILE=CANCERLIT L131 AND L2
 L149 (2)SEA FILE=DRUGU L132 AND L2
 L150 (0)SEA FILE=VETU L133 AND L2
 L151 (0)SEA FILE=VETB L134 AND L2
 L152 (2)SEA FILE=SCISEARCH L135 AND L2
 L153 (0)SEA FILE=CONF L136 AND L2
 L154 (0)SEA FILE=CONFSCI L137 AND L2
 L155 (0)SEA FILE=DISSABS L138 AND L2
 L156 (66)SEA L139 AND L2
 L157 (1)SEA FILE=HCAPLUS L58 AND L22
 L158 (0)SEA FILE=WPIX L60 AND L23
 L159 (0)SEA FILE=MEDLINE L62 AND L24
 L160 (0)SEA FILE=EMBASE L64 AND L25
 L161 (0)SEA FILE=BIOSIS L66 AND L26
 L162 (0)SEA FILE=PASCAL L68 AND L27
 L163 (0)SEA FILE=JICST-EPLUS L70 AND L28
 L164 (0)SEA FILE=LIFESCI L72 AND L29
 L165 (0)SEA FILE=CANCERLIT L74 AND L30
 L166 (0)SEA FILE=DRUGU L76 AND L31
 L167 (0)SEA FILE=VETU L78 AND L32
 L168 (0)SEA FILE=VETB L80 AND L33
 L169 (0)SEA FILE=SCISEARCH L82 AND L34
 L170 (0)SEA FILE=CONF L84 AND L35
 L171 (0)SEA FILE=CONFSCI L86 AND L36
 L172 (0)SEA FILE=DISSABS L88 AND L37
 L173 (1)SEA L89 AND L38
 L174 (1)SEA FILE=HCAPLUS L140 AND L22
 L175 (0)SEA FILE=WPIX L141 AND L23
 L176 (0)SEA FILE=MEDLINE L142 AND L24
 L177 (0)SEA FILE=EMBASE L143 AND L25
 L178 (0)SEA FILE=BIOSIS L144 AND L26
 L179 (0)SEA FILE=PASCAL L145 AND L27
 L180 (0)SEA FILE=JICST-EPLUS L146 AND L28
 L181 (0)SEA FILE=LIFESCI L147 AND L29
 L182 (0)SEA FILE=CANCERLIT L148 AND L30
 L183 (0)SEA FILE=DRUGU L149 AND L31
 L184 (0)SEA FILE=VETU L150 AND L32
 L185 (0)SEA FILE=VETB L151 AND L33
 L186 (0)SEA FILE=SCISEARCH L152 AND L34
 L187 (0)SEA FILE=CONF L153 AND L35
 L188 (0)SEA FILE=CONFSCI L154 AND L36
 L189 (0)SEA FILE=DISSABS L155 AND L37
 L190 (1)SEA L156 AND L38
 L191 (1)SEA L91 OR L157 OR L174
 L192 (0)SEA FILE=WPIX L93 OR L158 OR L175
 L193 (0)SEA FILE=MEDLINE L95 OR L159 OR L176

L194(0)SEA FILE=EMBASE L97 OR L160 OR L177
L195(0)SEA FILE=BIOSIS L99 OR L161 OR L178
L196(0)SEA FILE=PASCAL L101 OR L162 OR L179
L197(0)SEA FILE=JICST-EPLUS L103 OR L163 OR L180
L198(0)SEA FILE=LIFESCI L105 OR L164 OR L181
L199(0)SEA FILE=CANCERLIT L107 OR L165 OR L182
L200(0)SEA FILE=DRUGU L109 OR L166 OR L183
L201(0)SEA FILE=VETU L111 OR L167 OR L184
L202(0)SEA FILE=VETB L113 OR L168 OR L185
L203(0)SEA FILE=SCISEARCH L115 OR L169 OR L186
L204(0)SEA FILE=CONF L117 OR L170 OR L187
L205(0)SEA FILE=CONFSCI L119 OR L171 OR L188
L206(0)SEA FILE=DISSABS L121 OR L172 OR L189
L207 1 SEA ABB=ON PLU=ON L122 OR L173 OR L190

FILE 'STNGUIDE' ENTERED AT 08:58:56 ON 29 SEP 2005

FILE 'HCAPLUS' ENTERED AT 08:59:05 ON 29 SEP 2005
D IBIB ED AB L207

FILE 'STNGUIDE' ENTERED AT 08:59:05 ON 29 SEP 2005
D QUE L207

FILE HCAPLUS

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FILE COVERS 1907 - 29 Sep 2005 VOL 143 ISS 14
FILE LAST UPDATED: 28 Sep 2005 (20050928/ED)

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FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Sep 23, 2005 (20050923/UP).

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